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(54) Title: NOVEL SUBSTITUTED IMIDAZOLE COMPOUNDS

(57) Abstract

Novel 1,4,5-substituted imidazole compounds and compositions for use in therapy as cytokine inhibitors.

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NOVEL SUBSTITUTED IMIDAZOLE COMPOUNDS

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FIELD OF THE INVENTION:

This invention relates to a novel imidazole compounds, processes for the preparation thereof, the use thereof in treating cytokine mediated diseases and 10 pharmaceutical compositions for use in such therapy.

BACKGROUND OF THE INVENTION

Intracellular signal transduction is the means by which cells respond to extracellular stimuli. Regardless of the nature of the cell surface receptor (e. g. protein 15 tyrosine kinase or seven-transmembrane G-protein coupled), protein kinases and phosphatases along with phospholipases are the essential machinery by which the signal is further transmitted within the cell [Marshall, J. C. *Cell*, 80, 179-278 (1995)]. Protein kinases can be categorized into five classes with the two major classes being, tyrosine kinases and serine / threonine kinases depending upon whether the enzyme 20 phosphorylates its substrate(s) on specific tyrosine(s) or serine / threonine(s) residues [Hunter, T., *Methods in Enzymology (Protein Kinase Classification)* p. 3, Hunter, T.; Sefton, B. M.; eds. vol. 200, Academic Press; San Diego, 1991].

For most biological responses, multiple intracellular kinases are involved and an individual kinase can be involved in more than one signaling event. These kinases 25 are often cytosolic and can translocate to the nucleus or the ribosomes where they can affect transcriptional and translational events, respectively. The involvement of kinases in transcriptional control is presently much better understood than their effect on translation as illustrated by the studies on growth factor induced signal transduction involving MAP/ERK kinase [Marshall, C. J. *Cell*, 80, 179 (1995); Herskowitz, I. *Cell*, 30 80, 187 (1995); Hunter, T. *Cell*, 80, 225 (1995); Seger, R., and Krebs, E. G. *FASEB J.*, 726-735 (1995)].

While many signaling pathways are part of cell homeostasis, numerous 35 cytokines (e.g., IL-1 and TNF) and certain other mediators of inflammation (e.g., COX-2, and iNOS) are produced only as a response to stress signals such as bacterial lippopolysaccharide (LPS). The first indications suggesting that the signal transduction pathway leading to LPS-induced cytokine biosynthesis involved protein

kinases came from studies of Weinstein [Weinstein, *et al.*, *J. Immunol.*, **151**, 3829(1993)] but the specific protein kinases involved were not identified. Working from a similar perspective, Han [Han, *et al.*, *Science* **265**, 808(1994)] identified murine p38 as a kinase which is tyrosine phosphorylated in response to LPS. Definitive proof of the involvement of the p38 kinase in LPS-stimulated signal transduction pathway leading to the initiation of proinflammatory cytokine biosynthesis was provided by the independent discovery of p38 kinase by Lee [Lee, *et al.*, *Nature*, **372**, 739(1994)] as the molecular target for a novel class of anti-inflammatory agents. The discovery of p38 (termed by Lee as CSBP 1 and 2) provided a mechanism of action of a class of anti-inflammatory compounds for which SK&F 86002 was the prototypic example. These compounds inhibited IL-1 and TNF synthesis in human monocytes at concentrations in the low mM range [Lee, *et al.*, *Int. J. Immunopharmac.* **10**(7), 835(1988)] and exhibited activity in animal models which are refractory to cyclooxygenase inhibitors [Lee, *et al.*, *Annals N. Y. Acad. Sci.*, **696**, 149(1993)].

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MITOGEN AND STRESS ACTIVATED PROTEIN KINASE CASCADES

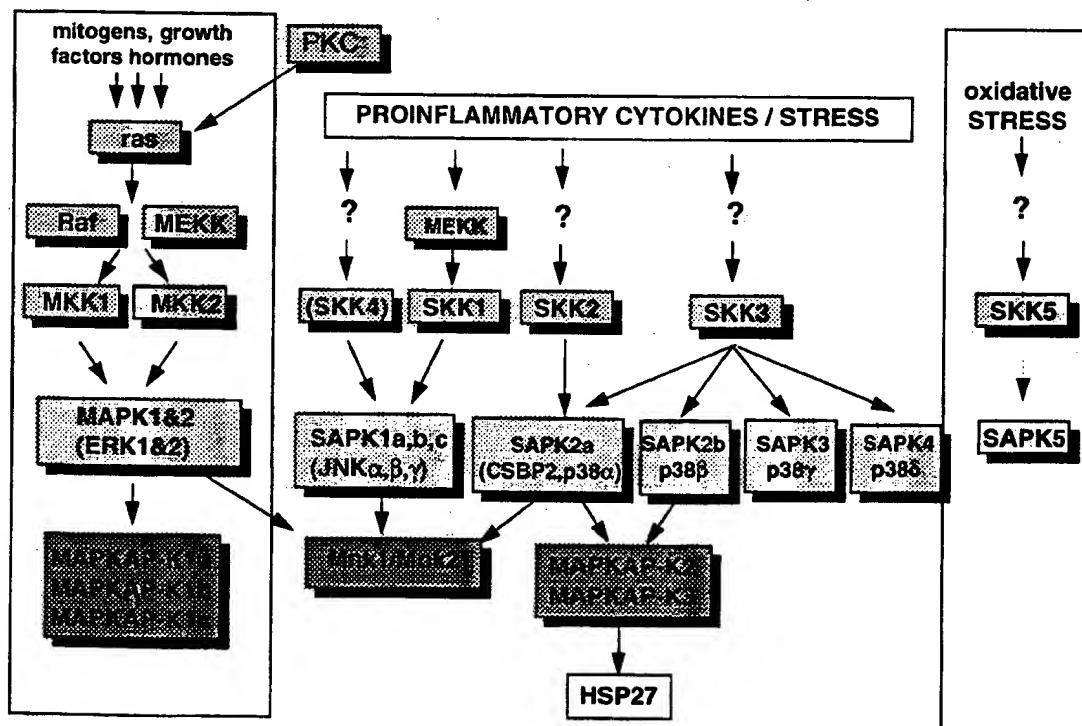


Figure 1

It is now firmly established that CSBP/p38 is a one of several kinases involved in a stress-response signal transduction pathway which is parallel to and largely

independent of the analogous mitogen-activated protein kinase (MAP) kinase cascade (Figure 1). Stress signals, including LPS, pro-inflammatory cytokines, oxidants, UV light and osmotic stress, activate kinases upstream from CSBP/p38 which in turn phosphorylate CSBP/p38 at threonine 180 and tyrosine 182 resulting in CSBP/p38 activation. MAPKAP kinase-2 and MAPKAP kinase-3 have been identified as downstream substrates of CSBP/p38 which in turn phosphorylate heat shock protein Hsp 27 (Figure 2). It is not yet known whether MAPKAP-2, MAPKAP-3, Mnk1 or Mnk2 are involved in cytokine biosynthesis or alternatively that inhibitors of CSBP/p38 kinase might regulate cytokine biosynthesis by blocking a yet unidentified substrate downstream from CSBP/p38 [Cohen, P. *Trends Cell Biol.*, 353-361(1997)].

p38 Kinase Pathway

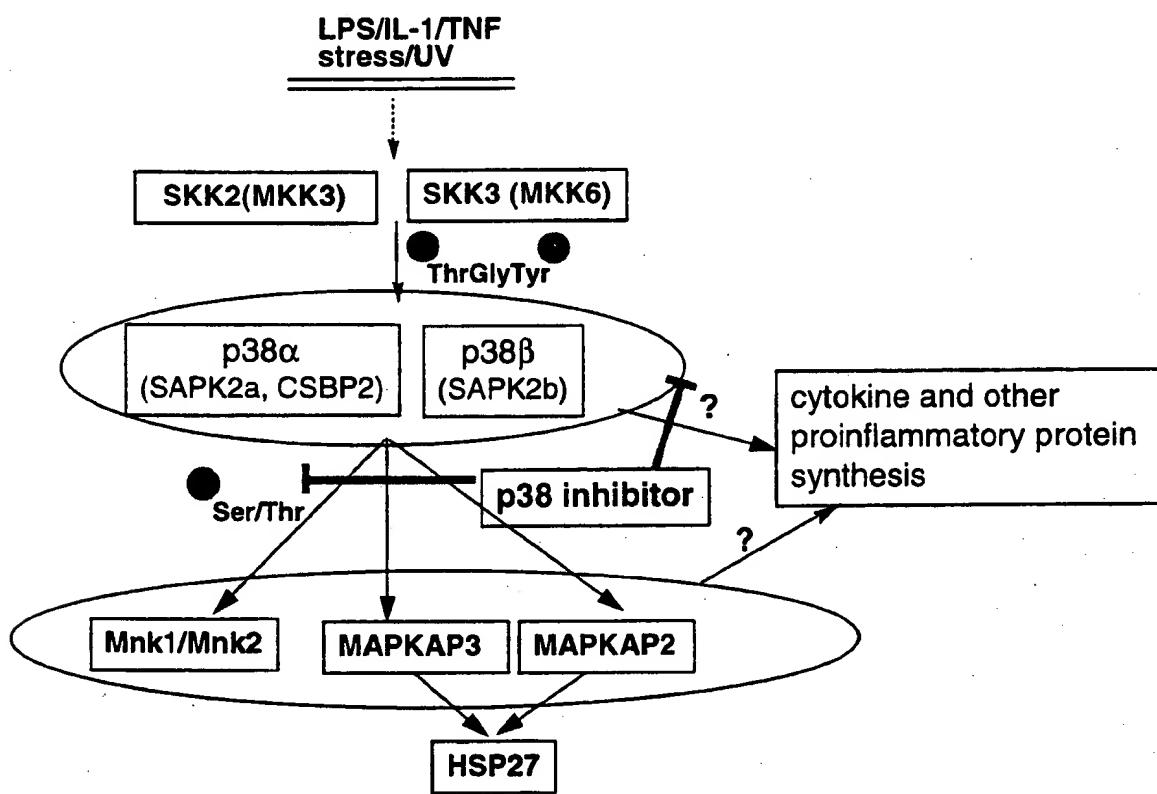


Figure 2

What is known, however, is that in addition to inhibiting IL-1 and TNF, 15 CSBP/p38 kinase inhibitors (SK&F 86002 and SB 203580) also decrease the synthesis of a wide variety of pro-inflammatory proteins including, IL-6, IL-8, GM-CSF and COX-2. Inhibitors of CSBP/p38 kinase have also been shown to suppress the TNF-induced expression of VCAM-1 on endothelial cells, the TNF-induced phosphorylation

and activation of cytosolic PLA2 and the IL-1-stimulated synthesis of collagenase and stromelysin. These and additional data demonstrate that CSBP/p38 is involved not only cytokine synthesis, but also in cytokine signaling [CSBP/P38 kinase reviewed in Cohen, P. Trends Cell Biol., 353-361(1997)].

5 Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are biological substances produced by a variety of cells, such as monocytes or macrophages. IL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g., Dinarello et al., Rev. Infect. Disease, 6, 51 (1984)]. The 10 myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

15 There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, 20 gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic β cells [review of the biological activities which have been attributed to IL-1 Dinarello, J. Clinical Immunology, 5 (5), 287-297 (1985)].

25 Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host 30 reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

35 Interleukin-8 (IL-8) is a chemotactic factor produced by several cell types including mononuclear cells, fibroblasts, endothelial cells, and keratinocytes. Its production from endothelial cells is induced by IL-1, TNF, or lipopolysaccharide

(LPS). IL-8 stimulates a number of functions in vitro. It has been shown to have chemoattractant properties for neutrophils, T-lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as well as lysozomal enzyme release and respiratory burst from neutrophils. IL-8 has also 5 been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis, this may contribute to increased adhesion of the neutrophils to vascular endothelial cells. Many diseases are characterized by massive neutrophil infiltration. Conditions associated with an increased in IL-8 production (which is responsible for chemotaxis of neutrophil into the inflammatory site) would 10 benefit by compounds which are suppressive of IL-8 production.

IL-1 and TNF affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease 15 states.

Inhibition of signal transduction via CSBP/p38, which in addition to IL-1, TNF and IL-8 described above is also required for the synthesis and/or action of several additional pro-inflammatory proteins (i.e., IL-6, GM-CSF, COX-2, collagenase and stromelysin), is expected to be a highly effective mechanism for regulating the 20 excessive and destructive activation of the immune system. This expectation is supported by the potent and diverse anti-inflammatory activities described for CSBP/p38 kinase inhibitors [Badger, *et al.*, *J. Pharm. Exp. Thera.* **279** (3): 1453-1461.(1996); Griswold, *et al.*, *Pharmacol. Comm.* **7**, 323-229 (1996)].

There remains a need for treatment, in this field, for compounds which are 25 cytokine suppressive anti-inflammatory drugs, i.e. compounds which are capable of inhibiting the CSBP/p38/RK kinase.

SUMMARY OF THE INVENTION

This invention relates to the novel compounds of Formula (I) and 30 pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable diluent or carrier.

This invention relates to a method of treating a CSBP/RK/p38 kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I).

35 This invention also relates to a method of inhibiting cytokines and the treatment of a cytokine mediated disease, in a mammal in need thereof, which

comprises administering to said mammal an effective amount of a compound of Formula (I).

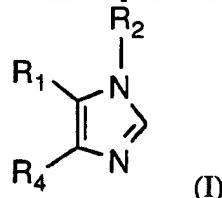
This invention more specifically relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to 5 said mammal an effective amount of a compound of Formula (I).

This invention more specifically relates to a method of inhibiting the production of IL-6 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

This invention more specifically relates to a method of inhibiting the 10 production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

This invention more specifically relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I).

15 Accordingly, the present invention provides a compound of Formula (I):



R1 is 4-pyridyl, pyrimidinyl, 4-pyridazinyl, 1,2,4-triazin-5-yl, quinolyl,

isoquinolinyl, quinazolin-4-yl, 1-imidazolyl or 1-benzimidazolyl ring, which 20 ring is substituted with Y-R_a and optionally with an additional independent substituent selected from C₁₋₄ alkyl, halogen, hydroxyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C₁₋₆ alkyl substituted amino, an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅, N(R₁₀)C(O)R_b or NHR_a;

25 Y is oxygen or sulfur;

R4 is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, C(Z)NR₇R₁₇, C(Z)OR₁₆,

30 (CR₁₀R₂₀)_vCOR₁₂, SR₅, SOR₅, OR₁₂, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, ZC(Z)R₁₂, NR₁₀C(Z)R₁₆, or (CR₁₀R₂₀)_vNR₁₀R₂₀ and which, for other positions of substitution, is halogen, cyano, C(Z)NR₁₃R₁₄, C(Z)OR₃, (CR₁₀R₂₀)_m"COR₃, S(O)_mR₃, OR₃, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl,

(CR₁₀R₂₀)_m"NR₁₀C(Z)R₃, NR₁₀S(O)_mR₈, NR₁₀S(O)_m'NR₇R₁₇, ZC(Z)R₃
or (CR₁₀R₂₀)_m"NR₁₃R₁₄;

v is 0, or an integer having a value of 1 or 2;

m is 0, or the integer 1 or 2;

5 m' is an integer having a value of 1 or 2,
m" is 0, or an integer having a value of 1 to 5;
R₂ is (CR₁₀R₂₃)_n' OR₉, heterocyclil, heterocyclilC₁₋₁₀ alkyl, C₁₋₁₀alkyl, halo-
substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl,
C₃₋₇cycloalkylC₁₋₁₀ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇cycloalkenyl-C₁₋₁₀-alkyl,
10 aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroaryl-C₁₋₁₀-alkyl, (CR₁₀R₂₃)_nOR₁₁,
(CR₁₀R₂₃)_nS(O)_mR₁₈, (CR₁₀R₂₃)_n'S(O)₂R₁₈, (CR₁₀R₂₃)_nNHS(O)₂R₁₈,
(CR₁₀R₂₃)_nS(O)_m'NR₁₃R₁₄, (CR₁₀R₂₃)_n NR₁₃R₁₄, (CR₁₀R₂₃)_nNO₂,
(CR₁₀R₂₃)_nCN, (CR₁₀R₂₃)_nC(Z)R₁₁, (CR₁₀R₂₃)_nOC(Z)R₁₁,
(CR₁₀R₂₃)_nC(Z)OR₁₁, (CR₁₀R₂₃)_nC(Z)NR₁₃R₁₄,
15 (CR₁₀R₂₃)_nNR₂₃C(Z)R₁₁, (CR₁₀R₂₃)_nC(Z)NR₁₁OR₉,
(CR₁₀R₂₃)_nN(OR₆)C(Z)NR₁₃R₁₄, (CR₁₀R₂₃)_nN(OR₆)C(Z)R₁₁,
(CR₁₀R₂₃)_nC(=NOR₆)R₁₁, (CR₁₀R₂₃)_nNR₂₃C(=NR₁₉)NR₁₃R₁₄,
(CR₁₀R₂₃)_nOC(Z)NR₁₃R₁₄, (CR₁₀R₂₃)_nNR₂₃C(Z)NR₁₃R₁₄,
(CR₁₀R₂₃)_nNR₂₃C(Z)OR₁₀, 5-(R₁₈)-1,2,4-oxadizaol-3-yl or
20 4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl,
arylalkyl, heteroaryl, heteroaryl alkyl, cycloalkyl, cycloalkyl alkyl, heterocyclic
and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

25 25 Z is oxygen or sulfur;

R_a is aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclilC₁₋₆ alkyl, heteroaryl,
heteroarylC₁₋₆alkyl, wherein each of these moieties may be optionally
substituted;

R_b is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl,
30 heteroarylC₁₋₄alkyl, heterocyclil, or heterocyclilC₁₋₄ alkyl, wherein each of
these moieties may be optionally substituted;

R₃ is heterocyclil, heterocyclilC₁₋₁₀ alkyl or R₈;

R₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₇R₁₇, excluding the
moieties SR₅ being SNR₇R₁₇ and SOR₅ being -SOH;

R₆ is hydrogen, a pharmaceutically acceptable cation, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄ alkyl, heterocyclyl, aroyl, or C₁₋₁₀ alkanoyl;

5 R₇ and R₁₇ is each independently selected from hydrogen or C₁₋₄ alkyl or R₇ and R₁₇ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅;

R₈ is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, (CR₁₀R₂₀)_nOR₁₁, (CR₁₀R₂₀)_nS(O)_mR₁₈, (CR₁₀R₂₀)_nNHS(O)₂R₁₈, (CR₁₀R₂₀)_nNR₁₃R₁₄; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

10 R₉ is hydrogen, C(Z)R₁₁ or optionally substituted C₁₋₁₀ alkyl, S(O)₂R₁₈, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl;

15 R₁₀ and R₂₀ is each independently selected from hydrogen or C₁₋₄ alkyl; R₁₁ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylC₁₋₁₀ alkyl, wherein these moieties may be optionally substituted;

R₁₂ is hydrogen or R₁₆;

20 R₁₃ and R₁₄ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉ ;

25 R₁₅ is R₁₀ or C(Z)-C₁₋₄ alkyl;

R₁₆ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₇ cycloalkyl;

R₁₈ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, aryl, arylC₁₋₁₀alkyl, heterocyclyl, heterocyclyl-C₁₋₁₀alkyl, heteroaryl or heteroarylC₁₋₁₀alkyl;

R₁₉ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl;

30 R₂₃ is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl moiety, all of which may be optionally substituted;

or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

In Formula (I), suitable R₁ moieties includes 4-pyridyl, 4-pyrimidinyl, 4-pyridazinyl, 1,2,4-triazin-5-yl, 4-quinolyl, 6-isoquinolinyl, 4-quinazolinyl, 1-imidazolyl and 1-benzimidazolyl rings, of which the 4-pyridyl, 4-pyrimidinyl and 4-quinolyl rings are preferred. More preferred is the 4-pyrimidinyl or 4-pyridyl moiety, and most preferred is the 4-pyrimidinyl ring.

The R₁ moiety is substituted with the -Y-R_a group wherein Y is oxygen or sulfur, and R_a is aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclicC₁₋₆alkyl, heteroaryl, or heteroarylC₁₋₆alkyl; and wherein each of the R_a moieties may be 10 optionally substituted as defined below.

When R_a is aryl, it is preferably phenyl or naphthyl. When R_a is arylalkyl, it is preferably benzyl or napthylmethyl. When R_a is a heterocyclic or heterocyclic alkyl moiety, the heterocyclic portion is preferably pyrrolindinyl, piperidine, morpholino, tetrahydropyran, tetrahydrothiopyranyl, tetrahydrothiopyransulfinyl, 15 tetrahydrothio-pyransulfonyl, pyrrolindinyl, indole, or piperonyl ring. It is noted that the heterocyclic rings herein may contain unsaturation, such as in a tryptamine ring.

When R_a is a heteroaryl ring as defined below, it is preferably a pyridine or tetrazole ring.

20 The R_a aryl, heterocyclic and heteroaryl rings may be optionally substituted one or more times, preferably one to three times, independently with halogen; C₁₋₄ alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted alkyl, such as CF₃; hydroxy or OR₁₁; hydroxy substituted C₁₋₄ alkyl; (CR₁₀R₂₀)_q C₁₋₄ alkoxy, such as methoxy or ethoxy; (CR₁₀R₂₀)_q S(O)_malkyl and; 25 (CR₁₀R₂₀)_qS(O)_m aryl (wherein m is 0, 1, or 2); (CR₁₀R₂₀)_qC(O)OR₁₁, such as C(O)C₁₋₄ alkyl or C(O)OH moieties; (CR₁₀R₂₀)_qC(O)R₁₁; (CR₁₀R₂₀)_qOC(O)R_c; -O-(CH₂)_s-O-, such as in a ketal or dioxoalkylene bridge; (CR₁₀R₂₀)_qNR₁₃R₁₄; (CR₁₀R₂₀)_qN(R₁₀)C(O)R_b; (CR₁₀R₂₀)_qC(O)NR₁₃R₁₄; (CR₁₀R₂₀)_qC(O)NR₁₀R_c; (CR₁₀R₂₀)_qS(O)₂NR₁₃R₁₄; 30 (CR₁₀R₂₀)_qS(O)₂NR₁₀R_c; (CR₁₀R₂₀)_qN(R₁₀)S(O)₂ R_c; cyano, nitro, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅; aryl, such as phenyl; an optionally substituted arylalkyl, such as benzyl or phenethyl; aryloxy, such as phenoxy; or arylalkyloxy such as benzyloxy; and wherein the aryl, arylalkyl, 35 aryloxy and arylalkyloxy moieties may be optionally substituted themselves one to

two times by halogen; hydroxy; hydroxy substituted alkyl; C₁-10 alkoxy; S(O)_malkyl; amino, NR₇R₁₇; C₁-4 alkyl, or halosubstituted C₁-4 alkyl.

Suitably, q is 0 or an integer having a value of 1 to 4.

R_b is suitably hydrogen, C₁-6 alkyl, C₃-7 cycloalkyl, aryl, arylC₁-4 alkyl, 5 heteroaryl, heteroarylC₁-4alkyl, heterocyclyl, or heterocyclylC₁-4 alkyl moiety; all of which may be optionally substituted as defined below.

R_c is suitably an C₁-6 alkyl, C₃-7 cycloalkyl, aryl, arylC₁-4 alkyl, heteroaryl, heteroarylC₁-4alkyl, heterocyclyl, or heterocyclylC₁-4 alkyl moiety, all of which may be optionally substituted as defined below.

10 Suitable R_a groups include, but are not limited to, benzyl, halosubstituted benzyl, naphylmethyl, phenyl, halosubstituted phenyl, aminocarbonylphenyl, alkylphenyl, cyanophenyl, alkylthiophenyl, hydroxyphenyl, alkoxyphenyl, phenoxyphenyl, benzyloxyphenyl, phenylphenyl, methylenedioxophenyl, trifluoromethylphenyl, methylsulfonylphenyl, tetrazole, methyltetrazolyl, 15 morpholinopropyl, piperonyl, piperidin-4-yl, alkyl substituted piperidine, such as 1-methyl piperidine, or 2,2,6,6-tetramethylpiperidin-4-yl.

It is recognized that the R₁ group may additionally be substituted one or more times independently by C₁-4 alkyl, halo, OH, C₁-4 alkoxy, C₁-4 alkylthio, C₁-4 alkylsulfinyl, CH₂OR₁₂, amino, mono- and di-C₁-6 alkylsubstituted amino, 20 N(R₁₀)C(O)R_b, NHR_a or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅.

When the additional R₁ optional substituent is N(R₁₀)C(O) R_b, R_b is 25 preferably C₁-6 alkyl; preferably R₁₀ is hydrogen. It is also recognized that the R_b moieties, in particular the C₁-6 alkyl group may be optionally substituted, preferably from one to three times, preferably with halogen, such as fluorine, as in trifluoromethyl or trifluoroethyl.

The preferred ring placement on the R₁ substituent for YR_a, on the 4-pyridyl derivative is the 2-position, and a preferred ring placement on the 4-pyrimidinyl ring 30 is also at the 2-position.

Suitably, R₄ is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is 35 optionally substituted by one or two substituents. More preferably R₄ is a phenyl or naphthyl ring. Suitable substitutions for R₄ when this is a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl moiety are one or two substituents each of which are independently selected from halogen, SR₅, SOR₅, OR₁₂, CF₃, or (CR₁₀R₂₀)_vNR₁₀R₂₀, and for other positions of substitution on these rings

preferred substitution is halogen, S(O)_mR₃, OR₃, CF₃, (CR₁₀R₂₀)_m'NR₁₃R₁₄, NR₁₀C(Z)R₃ and NR₁₀S(O)_m'R₈. Preferred substituents for the 4-position in phenyl and naphth-1-yl and on the 5-position in naphth-2-yl include halogen, especially fluoro and chloro and SR₅ and SOR₅ wherein R₅ is preferably a C₁₋₂ alkyl, more preferably methyl; of which the fluoro and chloro is more preferred, and most especially preferred is fluoro. Preferred substituents for the 3-position in phenyl and naphth-1-yl rings include: halogen, especially fluoro and chloro; OR₃, especially C₁₋₄ alkoxy; CF₃, NR₁₀R₂₀, such as amino; NR₁₀C(Z)R₃, especially NHCO(C₁₋₁₀ alkyl); NR₁₀S(O)_m'R₈, especially NHSO₂(C₁₋₁₀ alkyl), and SR₃ and -SOR₃ wherein R₃ is preferably a C₁₋₂ alkyl, more preferably methyl. When the phenyl ring is disubstituted preferably it is two independent halogen moieties, such as fluoro and chloro, preferably di-chloro and more preferably in the 3,4-position. It is also preferred that for the 3-position of both the OR₃ and ZC(Z)R₃ moieties, R₃ may also include hydrogen.

Preferably, the R₄ moiety is an unsubstituted or substituted phenyl moiety. More preferably, R₄ is phenyl or phenyl substituted at the 4-position with fluoro and/or substituted at the 3-position with fluoro, chloro, C₁₋₄ alkoxy, methanesulfonamido or acetamido, or R₄ is a phenyl di-substituted at the 3,4-position independently with chloro or fluoro, more preferably chloro. Most preferably, R₄ is a 4-fluorophenyl.

Suitably, Z is oxygen or sulfur, preferably oxygen.

Suitably, R₂ is (CR₁₀R₂₃)_n' OR₉, heterocyclyl, heterocyclylC₁₋₁₀ alkyl, C₁₋₁₀alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇cycloalkylC₁₋₁₀ alkyl, C₅₋₇ cycloalkenyl,

C₅₋₇cycloalkenyl-C₁₋₁₀-alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroaryl-C₁₋₁₀-alkyl, (CR₁₀R₂₃)_nOR₁₁, (CR₁₀R₂₃)_nS(O)_mR₁₈, (CR₁₀R₂₃)_n'S(O)₂R₁₈, (CR₁₀R₂₃)_nNHS(O)₂R₁₈, (CR₁₀R₂₃)_nS(O)_m'NR₁₃R₁₄, (CR₁₀R₂₃)_nNR₁₃R₁₄, (CR₁₀R₂₃)_nNO₂, (CR₁₀R₂₃)_nCN, (CR₁₀R₂₃)_nC(Z)R₁₁, (CR₁₀R₂₃)_nOC(Z)R₁₁, (CR₁₀R₂₃)_nC(Z)OR₁₁, (CR₁₀R₂₃)_nC(Z)NR₁₃R₁₄, (CR₁₀R₂₃)_nNR₂₃C(Z)R₁₁, (CR₁₀R₂₃)_nC(Z)NR₁₁OR₉, (CR₁₀R₂₃)_nN(OR₆)C(Z)NR₁₃R₁₄, (CR₁₀R₂₃)_nN(OR₆)C(Z)R₁₁, (CR₁₀R₂₃)_nC(=NOR₆)R₁₁, (CR₁₀R₂₃)_nNR₂₃C(=NR₁₉)NR₁₃R₁₄, (CR₁₀R₂₃)_nOC(Z)NR₁₃R₁₄, (CR₁₀R₂₃)_nNR₂₃C(Z)NR₁₃R₁₄, (CR₁₀R₂₃)_nNR₂₃C(Z)OR₁₀, 5-(R₁₈)-1,2,4-oxadizaol-3-yl or 4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl,

heteroaryl, heteroaryl alkyl, cycloalkyl, cycloalkyl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted.

Suitably n is an integer having a value of 1 to 10, m is 0, or the integer 1 or 2; n' is 0, or an integer having a value of 1 to 10; and m' is 1 or 2. Preferably n is 1 to 4.

Suitably, R₂₃ is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl moiety, all of which may be optionally substituted as defined below.

Preferably R₂ is an optionally substituted heterocyclyl ring, and optionally substituted heterocyclylC₁₋₁₀ alkyl, an optionally substituted C₁₋₁₀ alkyl, an optionally substituted C₃₋₇cycloalkyl, an optionally substituted C₃₋₇cycloalkyl C₁₋₁₀ alkyl, (CR₁₀R₂₃)_{n'} OR₉, (CR₁₀R₂₃)_nCN, (CR₁₀R₂₃)_nC(Z)OR₁₁ group, (CR₁₀R₂₃)_nNR₁₃R₁₄, (CR₁₀R₂₃)_nNR₁₀C(Z)R₁₁, (CR₁₀R₂₃)_nNHS(O)₂R₁₈, (CR₁₀R₂₀)_nS(O)_mR₁₈, an optionally substituted aryl; an optionally substituted arylC₁₋₁₀ alkyl, (CR₁₀R₂₃)_nOR₁₁, (CR₁₀R₂₃)_nC(Z)R₁₁, or (CR₁₀R₂₃)_nC(=NOR₆)R₁₁ group.

More preferably R₂ is an optionally substituted heterocyclyl ring, and optionally substituted heterocyclylC₁₋₁₀ alkyl, optionally substituted aryl, an optionally substituted C₃₋₇cycloalkyl, an optionally substituted C₃₋₇cycloalkyl C₁₋₁₀ alkyl, (CR₁₀R₂₃)_{n'} OR₉, (CR₁₀R₂₀)_nNR₁₃R₁₄, or (CR₁₀R₂₀)_nC(Z)OR₁₁ group.

When R₂ is an optionally substituted heterocyclyl the ring is preferably a morpholino, pyrrolidinyl, or a piperidinyl group. When the ring is optionally substituted the substituents may be directly attached to the free nitrogen, such as in the piperidinyl group or pyrrole ring, or on the ring itself. Preferably the ring is a piperidine or pyrrole, more preferably piperidine. The heterocyclyl ring may be optionally substituted one to four times independently by halogen; C₁₋₄ alkyl; aryl, such as phenyl; aryl alkyl, such as benzyl - wherein the aryl or aryl alkyl moieties themselves may be optionally substituted (as in the definition section below); C(O)OR₁₁, such as the C(O)C₁₋₄ alkyl or C(O)OH moieties; C(O)H; C(O)C₁₋₄ alkyl, hydroxy substituted C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, S(O)_mC₁₋₄ alkyl (wherein m is 0, 1, or 2), NR₁₀R₂₀ (wherein R₁₀ and R₂₀ are independently hydrogen or C₁₋₄alkyl).

Preferably if the ring is a piperidine, the ring is attached to the imidazole at the 4-position, and the substituents are directly on the available nitrogen, i.e. a 1-Formyl-4-piperidine, 1-benzyl-4-piperidine, 1-methyl-4-piperidine, 1-

ethoxycarbonyl-4-piperidine. If the ring is substituted by an alkyl group and the ring is attached in the 4-position, it is preferably substituted in the 2- or 6- position or both, such as 2,2,6,6-tetramethyl-4-piperidine. Similarly, if the ring is a pyrrole, the ring is attached to the imidazole at the 3-position, and the substituents are all directly on the available nitrogen.

When R₂ is an optionally substituted heterocyclyl C₁-10 alkyl group, the ring is preferably a morpholino, pyrrolidinyl, or a piperidinyl group. Preferably this alkyl moiety is from 1 to 4, more preferably 3 or 4, and most preferably 3, such as in a propyl group. Preferred heterocyclic alkyl groups include but are not limited to, 10 morpholino ethyl, morpholino propyl, pyrrolidinyl propyl, and piperidinyl propyl moieties. The heterocyclic ring herein is also optionally substituted in a similar manner to that indicated above for the direct attachment of the heterocyclyl.

When R₂ is an optionally substituted C₃-7cycloalkyl, or an optionally substituted C₃-7cycloalkyl C₁-10 alkyl, the cycloalkyl group is preferably a C₄ or C₆ ring, most preferably a C₆ ring; which ring is optionally substituted. The cycloalkyl ring may be optionally substituted one to three times independently by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; C₁-10 alkoxy, such as methoxy or ethoxy; S(O)_m alkyl, wherein m is 0, 1, or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; S(O)_m aryl; cyano, nitro, amino, mono & di-20 substituted amino, such as in the NR₇R₁₇ group, wherein R₇ and R₁₇ are as defined in Formula (I), or where the R₇R₁₇ may cyclize together with the nitrogen to which they are attached to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from oxygen, sulfur or NR₁₅ (and R₁₅ is as defined for Formula (I)); N(R₁₀)C(O)X₁(wherein R₁₀ is as defined for Formula (I)), and 25 X₁ is C₁-4 alkyl, aryl or arylC₁-4alkyl); N(R₁₀)C(O) aryl; C₁-10 alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; optionally substituted alkyl wherein the substituents are halogen, (such as CF₃), hydroxy, nitro, cyano, amino, mono & di-30 substituted amino, such as in the NR₇R₁₇ group, S(O)_m alkyl and S(O)_m aryl, wherein m is 0, 1 or 2; optionally substituted alkylene, such as ethylene or propylene; optionally substituted alkyne, such as ethyne; C(O)OR₁₁ (wherein R₁₁ is as defined in Formula (I)), such as the free acid or methyl ester derivative; the group R_e; -C(O)H; =O; =N-OR₁₁; -N(H)-OH (or substituted alkyl or aryl derivatives thereof on the nitrogen or the oxime moiety); - N(OR_d)-C(O)-R_f; an optionally substituted aryl, such as phenyl; an optionally substituted arylC₁-4alkyl, such as 35 benzyl or phenethyl; an optionally substituted heterocycle or heterocyclic C₁-4alkyl, and further these aryl, arylalkyl, heterocyclic, and heterocyclic alkyl moieties are

optionally substituted one to two times by halogen, hydroxy, C₁-10 alkoxy, S(O)malkyl, cyano, nitro, amino, mono & di-substituted amino, such as in the NR₇R₁₇ group, an alkyl, halosubstituted alkyl.

Suitably R_d is hydrogen, a pharmaceutically acceptable cation, aroyl or a

5 C₁-10 alkanoyl group.

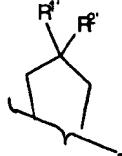
Suitably R_e is a 1,3-dioxyalkylene group of the formula -O-(CH₂)_s-O-, wherein s is 1 to 3, preferably s is 2 yielding a 1,3-dioxyethylene moiety, or ketal functionality. Suitably R_f is NR₂₁R₂₂; alkyl 1-6; halosubstituted alkyl 1-6; hydroxy substituted alkyl 1-6; alkenyl 2-6; aryl or heteroaryl optionally substituted by halogen, alkyl 1-6, halosubstituted alkyl 1-6, hydroxyl, or alkoxy 1-6.

Suitably R₂₁ is hydrogen, or alkyl 1-6.

Suitably R₂₂ is hydrogen, alkyl 1-6, aryl, benzyl, heteroaryl, alkyl substituted by halogen or hydroxyl, or phenyl substituted by a member selected from the group consisting of halo, cyano, alkyl 1-12, alkoxy 1-6, halosubstituted alkyl 1-6, alkylthio, 15 alkylsulphonyl, or alkylsulfinyl; or R₂₁ and R₂₂ may together with the nitrogen to which they are attached form a ring having 5 to 7 members, which members may be optionally replaced by a heteroatom selected from oxygen, sulfur or nitrogen. The ring may be saturated or contain more than one unsaturated bond. Preferably R_f is NR₂₁R₂₂, and more preferably R₂₁ and R₂₂ are both hydrogen.

20 When the R₂ cycloalkyl moiety is substituted by NR₇R₁₇ group, or NR₇R₁₇ C₁-10 alkyl group, and the R₇ and R₁₇ are as defined in Formula (I), the substituent is preferably an amino, amino alkyl, or an optionally substituted pyrrolidinyl moiety.

A preferred ring placement on the cycloalkyl moiety is the 4-position, such as in a C₆ ring. When the cycloalkyl ring is di-substituted it is preferably di-substituted at the 4 position, such as in:



wherein R^{1'} and R^{2'} are independently the optional substitutents indicated above for R₂. Preferably, R^{1'} and R^{2'} are hydrogen, hydroxy, alkyl, substituted alkyl, optionally substituted alkyne, aryl, arylalkyl, NR₇R₁₇, and N(R₁₀)C(O)R₁₁.

30 Suitably, alkyl is C₁-4 alkyl, such as methyl, ethyl, or isopropyl; NR₇R₁₇ and NR₇R₁₇ alkyl, such as amino, methylamino, aminomethyl, aminoethyl; substituted alkyl such as in cyanomethyl, cyanoethyl, nitroethyl, pyrrolidinyl; aryl such as in

phenyl; arylalkyl, such as in benzyl; optionally substituted alkyne, such as ethyne or propynyl; or together R^{1'} and R^{2'} are a keto functionality.

When R₂ is (CR₁₀R₂₀)_nNR₁₃R₁₄, R₁₃ and R₁₄ are as defined in Formula (I), that is R₁₃ and R₁₄ are each independently selected from hydrogen, optionally substituted C₁₋₄ alkyl, optionally substituted aryl or an optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉. It is recognized that in some instances this can yield the same moiety as a heterocyclic C₁₋₁₀ alkyl moiety noted above which is also a suitable R₂ variable. Preferably R₁₃ and R₁₄ are independently hydrogen, C₁₋₄ alkyl, preferably methyl, or benzyl. The n term is preferably 1 to 4, more preferably 3 or 4, and most preferably 3, such as in a propyl group. Preferred groups include, but are not limited to, aminopropyl, (N-methyl-N-benzyl)aminopropyl, (N-Phenylmethyl)amino-1-propyl, or diethylamino propyl.

When R₂ is a (CR₁₀R₂₀)_nC(Z)OR₁₁ group, R₁₁ is suitably hydrogen, C₁₋₄ alkyl, especially methyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group. Preferred groups include, but are not limited to, carboxymethyl-1-butyl, carboxy-1-propyl, or 2-acetoxyethyl.

When R₂ is a (CR₁₀R₂₀)_nS(O)_mR₁₈ group m is 0, 1, or 2, and R₁₈ is preferably aryl, especially phenyl, or C₁₋₁₀ alkyl, especially methyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group.

When R₂ is a (CR₁₀R₂₀)_nOR₁₁ group, R₁₁ is suitably hydrogen, aryl, especially phenyl, or C₁₋₁₀ alkyl, especially methyl or ethyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group.

When R₂ is a (CR₁₀R₂₀)_nNHS(O)₂R₁₈ group, R₁₈ is suitably alkyl, especially methyl. The n term is preferably 1 to 4, more preferably 2 or 3, such as in an ethyl or propyl group.

When R₂ is a optionally substituted aryl, the aryl is preferably phenyl. The aryl ring may be optionally substituted one or more times, preferably by one or two substituents, independently selected from C₁₋₄ alkyl, halogen, especially fluoro or chloro, (CR₁₀R₂₀)_tOR₁₁, (CR₁₀R₂₀)_tNR₁₀R₂₀, especially amino or mono- or di-alkylamino; (CR₁₀R₂₀)_tS(O)_mR₁₈, wherein m is 0, 1 or 2; SH, (CR₁₀R₂₀)_nNR₁₃R₁₄; NR₁₀C(Z)R₃ (such NHCO(C₁₋₁₀ alkyl)); NR₁₀S(O)_mR₈ (such as NHSO₂(C₁₋₁₀ alkyl)); and t is 0, or an integer of 1 to 4. Preferably the phenyl is substituted in the 3 or 4- position by (CR₁₀R₂₀)_tS(O)_mR₁₈, and R₁₈ is preferably C₁₋₁₀ alkyl, especially methyl.

When R₂ is an optionally substituted heteroaryl or heteroarylalkyl group the ring may be optionally substituted one or more times, preferably by one or two substituents, independently selected from one or more times, by C₁₋₄ alkyl, halogen, especially fluoro or chloro, (CR₁₀R₂₀)_tOR₁₁, (CR₁₀R₂₀)_tNR₁₀R₂₀, especially 5 amino or mono- or di-alkylamino (CR₁₀R₂₀)_tS(O)_mR₁₈, wherein m is 0, 1 or 2; SH, (CR₁₀R₂₀)_n-NR₁₃R₁₄, NR₁₀C(Z)R₃ (such NHCO(C₁₋₁₀ alkyl)); NR₁₀S(O)_mR₈ (such as NHSO₂(C₁₋₁₀ alkyl)); t is 0, or an integer of 1 to 4.

One skilled in the art would readily recognize that when R₂ is a (CR₁₀R₂₀)_nOC(Z)R₁₁, or (CR₁₀R₂₀)_nOC(Z)NR₁₃R₁₄ moiety, or any similarly 10 substituted group that n is preferably at least 2 which will allow for the synthesis of stable compounds.

Preferably R₂ is a C₁₋₄ alkyl (branched and unbranched), especially methyl, 15 methylthio propyl, a methylsulfinyl propyl, an amino propyl, N-methyl-N-benzylamino propyl group, diethylamino propyl, cyclopropyl methyl, morpholiny butyl, morpholiny propyl, a morpholiny ethyl, a piperidine or a substituted 20 piperidine. More preferably R₂ is a methyl, isopropyl, butyl, t-butyl, n-propyl, methylthiopropyl, or methylsulfinyl propyl, morpholino propyl, morpholiny butyl, phenyl substituted by halogen, thioalkyl or sulfinyl alkyl such as a methylthio, methylsulfinyl or methylsulfonyl moiety; piperidinyl, 1-Formyl-4-piperidine, 1-benzyl-4-piperidine, 1-methyl-4-piperidine, or a 1-ethoxycarbonyl-4-piperidine.

In all instances herein where there is an alkenyl or alkynyl moiety as a substituent group, the unsaturated linkage, i.e., the vinylene or acetylene linkage is preferably not directly attached to the nitrogen, oxygen or sulfur moieties, for instance in OR₃, or for certain R₂ moieties.

As used herein, "optionally substituted" unless specifically defined shall 25 mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted C₁₋₁₀alkyl; C₁₋₁₀ alkoxy, such as methoxy or ethoxy; halosubstituted C₁₋₁₀ alkoxy; S(O)_m alkyl, wherein m is 0, 1 or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; amino, mono & di-substituted C₁₋₁₀ alkyl 30 amino, such as in the NR₇R₁₇ group; or where the R₇R₁₇ may together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C₁₋₁₀ alkyl, C₃₋₇cycloalkyl, or C₃₋₇cycloalkyl C₁₋₁₀ alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; halosubstituted C₁₋₁₀ alkyl, such 35 CF₂CF₂H, or CF₃; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, wherein these aryl moieties may

also be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C₁-10 alkoxy; S(O)_m alkyl; amino, mono & di-substituted amino, such as in the NR₇R₁₇ group; alkyl, or CF₃.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The following terms, as used herein, refer to:

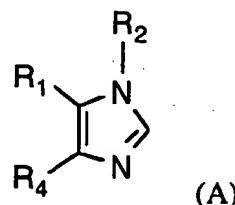
- "halo" or "halogens", include the halogens: chloro, fluoro, bromo and iodo.
- "C₁-10alkyl" or "alkyl" - both straight and branched chain radicals of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- "cycloalkyl" is used herein to mean cyclic radicals, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- "cycloalkenyl" is used herein to mean cyclic radicals, preferably of 5 to 8 carbons, which have at least one bond including but not limited to cyclopentenyl, cyclohexenyl, and the like.
- "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline,

isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, tetrazole, triazole, imidazole, or benzimidazole.

- "heterocyclic" (on its own or in any combination, such as "heterocyclylalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydro pyran, or imidazolidine.
- 5 • "aralkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C1-4 alkyl as defined above attached to an aryl, heteroaryl or heterocyclic moiety as also defined herein unless otherwise indicate.
- 10 • "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized S (O)2 moiety.
- 15 • "aryoyl" - a C(O)Ar, wherein Ar is as phenyl, naphthyl, or aryl alkyl derivative such as defined above, such group include but are not limited to benzyl and phenethyl.
- 15 • "alkanoyl" - a C(O)C1-10 alkyl wherein the alkyl is as defined above.

It is recognized that the compounds of the present invention may exist as stereoisomers, regioisomers, or diastereomers. These compounds may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

25 Yet another aspect of the present invention are the novel compounds of formula (A) represented by the structure:



30 R1 is 4-pyridyl, pyrimidinyl, 4-pyridazinyl, 1,2,4-triazin-5-yl, quinolyl, isoquinolinyl, quinazolin-4-yl ring, which ring is substituted with Y-R_a and optionally with an additional independent substituent selected from C1-4 alkyl, halogen, hydroxyl, C1-4 alkoxy, C1-4 alkylthio, C1-4 alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C1-6 alkyl substituted amino, an N-heterocycl ring which

ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅, N(R₁₀)C(O)R_b or NHR_b;

Y is oxygen or sulfur;

R₄ is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, C(Z)NR₇R₁₇, C(Z)OR₁₆, (CR₁₀R₂₀)_vCOR₁₂, SR₅, SOR₅, OR₁₂, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, ZC(Z)R₁₂, NR₁₀C(Z)R₁₆, or (CR₁₀R₂₀)_vNR₁₀R₂₀ and which, for other positions of substitution, is halogen, cyano, C(Z)NR₁₃R₁₄, C(Z)OR₃, (CR₁₀R₂₀)_m"COR₃, S(O)_mR₃, OR₃, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, (CR₁₀R₂₀)_m"NR₁₀C(Z)R₃, NR₁₀S(O)_mR₈, NR₁₀S(O)_m"NR₇R₁₇, ZC(Z)R₃ or (CR₁₀R₂₀)_m"NR₁₃R₁₄;

v is 0, or an integer having a value of 1 or 2;

15 m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2,

m" is 0, or an integer having a value of 1 to 5;

R₂ is (CR₁₀R₂₃)_n' OR₉, heterocyclyl, heterocyclylC₁₋₁₀ alkyl, C₁₋₁₀alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl,

20 C₃₋₇cycloalkylC₁₋₁₀ alkyl, C₅₋₇ cycloalkenyl, C₅₋₇cycloalkenyl-C₁₋₁₀-alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroaryl-C₁₋₁₀-alkyl, (CR₁₀R₂₃)_nOR₁₁, (CR₁₀R₂₃)_nS(O)_mR₁₈, (CR₁₀R₂₃)_nS(O)₂R₁₈, (CR₁₀R₂₃)_nNHS(O)₂R₁₈, (CR₁₀R₂₃)_nS(O)_m'NR₁₃R₁₄, (CR₁₀R₂₃)_n NR₁₃R₁₄, (CR₁₀R₂₃)_nNO₂, (CR₁₀R₂₃)_nCN, (CR₁₀R₂₃)_nC(Z)R₁₁, (CR₁₀R₂₃)_nOC(Z)R₁₁,

25 (CR₁₀R₂₃)_nC(Z)OR₁₁, (CR₁₀R₂₃)_nC(Z)NR₁₃R₁₄, (CR₁₀R₂₃)_nNR₂₃C(Z)R₁₁, (CR₁₀R₂₃)_nC(Z)NR₁₁OR₉, (CR₁₀R₂₃)_nN(OR₆)C(Z)NR₁₃R₁₄, (CR₁₀R₂₃)_nN(OR₆)C(Z)R₁₁, (CR₁₀R₂₃)_nC(=NOR₆)R₁₁, (CR₁₀R₂₃)_nNR₂₃C(=NR₁₉)NR₁₃R₁₄, (CR₁₀R₂₃)_nOC(Z)NR₁₃R₁₄, (CR₁₀R₂₃)_nNR₂₃C(Z)NR₁₃R₁₄,

30 (CR₁₀R₂₃)_nNR₂₃C(Z)OR₁₀, 5-(R₁₈)-1,2,4-oxadizaol-3-yl or 4-(R₁₂)-5-(R₁₈R₁₉)-4,5-dihydro-1,2,4-oxadiazol-3-yl; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, cycloalkyl, cycloalkyl alkyl, heterocyclic and heterocyclic alkyl groups may be optionally substituted;

n is an integer having a value of 1 to 10;

35 n' is 0, or an integer having a value of 1 to 10;

Z is oxygen or sulfur;

R_a is aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclC₁₋₆ alkyl, heteroaryl, or heteroarylC₁₋₆alkyl, wherein each of these moieties is optionally substituted by OR_{11'}, or R_a is an optionally substituted tetrahydronaphthalyl;

R_b is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocycl, or heterocyclC₁₋₄ alkyl, wherein each of these moieties may be optionally substituted;

R₃ is heterocycl, heterocyclC₁₋₁₀ alkyl or R₈;

R₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₇R₁₇, excluding the moieties SR₅ being SNR₇R₁₇ and SOR₅ being SOH;

R₆ is hydrogen, a pharmaceutically acceptable cation, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocycl, aroyl, or C₁₋₁₀ alkanoyl;

R₇ and R₁₇ is each independently selected from hydrogen or C₁₋₄ alkyl or R₇ and R₁₇ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅;

R₈ is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, (CR₁₀R₂₀)_nOR₁₁, (CR₁₀R₂₀)_nS(O)_mR₁₈, (CR₁₀R₂₀)_nNHS(O)₂R₁₈, (CR₁₀R₂₀)_nNR₁₃R₁₄; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R₉ is hydrogen, C(Z)R₁₁ or optionally substituted C₁₋₁₀ alkyl, S(O)₂R₁₈, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl;

R₁₀ and R₂₀ is each independently selected from hydrogen or C₁₋₄ alkyl;

R₁₁ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocycl, heterocyclC₁₋₁₀ alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylC₁₋₁₀ alkyl, wherein these moieties may be optionally substituted;

R_{11'} is C₃₋₇ cycloalkyl, heterocycl, heterocyclC₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylC₁₋₁₀ alkyl, wherein these moieties may be optionally substituted;

R₁₂ is hydrogen or R₁₆;

R₁₃ and R₁₄ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉;

R₁₅ is R₁₀ or C(Z)-C₁₋₄ alkyl;

R₁₆ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₇ cycloalkyl;

R₁₈ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, aryl, aryl-C₁₋₁₀ alkyl, heterocyclyl, heterocyclyl-C₁₋₁₀ alkyl, heteroaryl or heteroaryl-C₁₋₁₀ alkyl;

5 R₁₉ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl;

R₂₃ is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, aryl-C₁₋₄ alkyl, heteroaryl, heteroaryl-C₁₋₄ alkyl, heterocyclyl, or heterocyclyl-C₁₋₄ alkyl moiety, all of which may be optionally substituted;

or a pharmaceutically acceptable salt thereof.

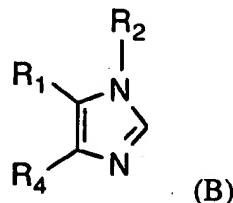
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The representative substituents of compounds of Formula (A) are the same as those described above for compounds Formula (I) except for the R₁ substituent group Y-R_a which is defined in formula (A). The R_a term must be substituted by OR₁₁ or R_a may be an optionally substituted tetrahydronaphthyl derivative, which 15 derivative may be attached to the Y group (oxygen or sulfur) in either the saturated or unsaturated ring. All of the R_a terms may additionally be optionally substituted as defined herein for formula (I).

Another aspect of the present invention is the pharmaceutical compositions comprising a compound of Formula (A) and a pharmaceutically acceptable carrier or 20 diluent thereof. Compounds of Formula (A) are also useful in the treatment of CSBP kinase mediated diseases as defined herein.

Another aspect of the present invention are the novel compounds of Formula (B) represented by the structure:

25



R₁ is 4-pyridyl, pyrimidinyl, 4-pyridazinyl, 1,2,4-triazin-5-yl, quinolyl, isoquinolinyl, or quinazolin-4-yl ring, which ring is substituted with Y-R_a and 30 optionally with an additional independent substituent selected from C₁₋₄ alkyl, halogen, hydroxyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C₁₋₆ alkyl substituted amino, an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅, N(R₁₀)C(O)R_b or NH R_a;

Y is oxygen or sulfur;

R₄ is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, C(Z)NR₇R₁₇, C(Z)OR₁₆, (CR₁₀R₂₀)_vCOR₁₂, SR₅, SOR₅, OR₁₂, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, ZC(Z)R₁₂, NR₁₀C(Z)R₁₆, or (CR₁₀R₂₀)_vNR₁₀R₂₀ and which, for other positions of substitution, is halogen, cyano, C(Z)NR₁₃R₁₄, C(Z)OR₃, (CR₁₀R₂₀)_m"COR₃, S(O)_mR₃, OR₃, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, (CR₁₀R₂₀)_m"NR₁₀C(Z)R₃, NR₁₀S(O)_m'R₈, NR₁₀S(O)_m'NR₇R₁₇, ZC(Z)R₃ or (CR₁₀R₂₀)_m"NR₁₃R₁₄;

5 v is 0, or an integer having a value of 1 or 2;

m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2,

10 m" is 0, or an integer having a value of 1 to 5;

R₂ is (CR₁₀R₂₃)_nNR₂₃C(Z)R₁₁;

n is an integer having a value of 1 to 10;

n' is 0, or an integer having a value of 1 to 10;

Z is oxygen or sulfur;

15 R_a is aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclC₁₋₆ alkyl, heteroaryl, heteroarylC₁₋₆alkyl or tetrahydronaphthyl, wherein each of these moieties may be optionally substituted;

R_b is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocycl, or heterocyclC₁₋₄ alkyl, wherein each of

20 these moieties may be optionally substituted;

R₃ is heterocycl, heterocyclC₁₋₁₀ alkyl or R₈;

R₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₇R₁₇, excluding the moieties SR₅ being SNR₇R₁₇ and SOR₅ being SOH;

R₇ and R₁₇ is each independently selected from hydrogen or C₁₋₄ alkyl or R₇ and

25 R₁₇ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅;

R₈ is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl, heteroarylC₁₋₁₀ alkyl, (CR₁₀R₂₀)_nOR₁₁, (CR₁₀R₂₀)_nS(O)_mR₁₈, (CR₁₀R₂₀)_nNHS(O)₂R₁₈,

30

35

(CR₁₀R₂₀)_nNR₁₃R₁₄; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R₉ is hydrogen, C(Z)R₁₁ or optionally substituted C₁₋₁₀ alkyl, S(O)₂R₁₈, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl;

5 R₁₀ and R₂₀ is each independently selected from hydrogen or C₁₋₄ alkyl;

R₁₁ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylC₁₋₁₀ alkyl, wherein these moieties may be optionally substituted;

R_{11'} is a C₁₋₁₀ alkyl which is substituted by C(O)OR₁₁, C(O)R₁₁, or OC(O)R₁₁;

10 R₁₂ is hydrogen or R₁₆;

R₁₃ and R₁₄ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉;

15 R₁₅ is R₁₀ or C(Z)-C₁₋₄ alkyl;

R₁₆ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₇ cycloalkyl;

R₁₈ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, aryl, arylC₁₋₁₀alkyl, heterocyclyl, heterocyclyl-C₁₋₁₀alkyl, heteroaryl or heteroarylC₁₋₁₀alkyl;

20 R₂₃ is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl moiety, all of which may be optionally substituted;

or a pharmaceutically acceptable salt thereof.

25 Representative substituents of compounds of Formula (B) are the same as those of Formula (I) except for the R₂ term which is defined in Formula (B). Another aspect of the present invention is the pharmaceutical compositions comprising a compound of Formula (B) and a pharmaceutically acceptable carrier or diluent thereof. Compounds of Formula (B) are also useful in the treatment of CSBP

30 kinase mediated diseases as defined herein.

Exemplified compounds of Formula (I) include:

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[(2-acetamidophenoxy)pyrimidin-4-yl]imidazole

35 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[(3-propionamidophenoxy)pyrimidin-4-yl]imidazole

1-Cyclohexyl-4-(4-fluorophenyl)-5-[(2-phenoxy)pyrimidin-4-yl]imidazole

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(2,6-dimethylphenoxy)pyrimidin-4-yl]imidazole

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(2-methylphenoxy)pyrimidin-4-yl]imidazole

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(2,6-dimethyl-4-chlorophenoxy)pyrimidin-4-yl]imidazole

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(indol-4-yloxy)pyrimidin-4-yl]imidazole

1-Cyclopropyl-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

10 1-Isopropyl-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

1-Cyclopentyl-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

(+/-)-1-(1-Hydroxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

3-[4-(4-Fluorophenyl)-5-[(2-phenoxy)pyrimidin-4-yl]imidazol-1-yl] propionitrile

15 (R)-(1-Hydroxy-3-phenylprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

(S)-(1-Hydroxy-3-phenylprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

(+/-)-1-(1-Phenoxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

20 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(3-piperazin-1-ylacetamido)phenoxy]pyrimidin-4-yl]imidazole

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(3-piperazin-1-ylamidophenoxy)pyrimidin-4-yl]imidazole; or

25 pharmaceutically acceptable salts thereof.

The present invention is also to the additional compounds of Formula (I) as shown and described in the Synthetic Example Section herein.

30 Additional exemplified compounds include:

1-Isopropyl-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxyphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxymethylphenoxy)pyrimidin-4-yl]imidazole

35

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2,5-dimethylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,5-dimethylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxyethylphenoxy)pyrimidin-4-yl]imidazole

5 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxypropylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,4-dimethylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2,3-dimethylphenoxy)pyrimidin-4-yl]imidazole

10 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,4-dichlorophenoxy)pyrimidin-4-yl]imidazole.

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-trifluoromethylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-chlorophenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-t-butylphenoxy)pyrimidin-4-yl]imidazole

15 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyrimidin-4-yl]imidazole.

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-isopropylphenoxy)pyrimidin-4-yl]imidazole.

1-(Piperidin-4-yl)-4-(4-fluorophenoxy)-5-[2-(2,4-dimethylphenoxy)pyrimidin-4-yl]imidazole

1-(4-Hydroxymethylcyclohexyl)-4-(4-fluorophenyl)-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]imidazole

20 1-(4-Hydroxymethylcyclohexyl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-methylcarboxamido-phenoxy)pyrimidin-4-yl]imidazole

25 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-carboxamidophenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-dimethylcarboxamido-phenoxy)pyrimidin-4-yl]imidazole

30 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-piperidinylcarboxamido-phenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-isopropylcarboxamidophenoxy)pyrimidin-4-yl]imidazole; or

a pharmaceutically acceptable salt thereof.

35 Another aspect of the present invention are the novel compounds, and pharmaceutical compositions of the following compounds as shown and described in

the Synthetic Example Section herein. All of these compounds are useful in the method of treatment of CSBP kinase mediated diseases as described herein.

- 5 N-[2-[4-(4-fluorophenyl)-5-[2-(4-fluoro)phenoxy]pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-3,4-dimethoxybenzamide
- 10 N-[2-[4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide
- 15 N-[2-[4-(4-fluorophenyl)-5-[(2-trifluoroethoxy)pyrimidin-4-yl]]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide
- 20 N-[2-[4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyrimidin-4-yl]]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide
- 25 N-[2-[4-(4-fluorophenyl)-5-[2-(4-benzyloxyphenoxy)pyrimidin-4-yl]]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide
- 30 N-[2-[4-(4-fluorophenyl)-5-[(2-cyclohexyl)ethoxy]pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide; or
a pharmaceutically acceptable salt thereof.

20 Another aspect of the present invention are the novel compounds or pharmaceutically acceptable salts thereof, and pharmaceutical compositions of the compounds of Table 1, wherein X is oxygen or sulfur, although only X=oxygen is shown therein. All of these exemplified compounds are useful in the method of treatment of CSBP kinase mediated diseases.

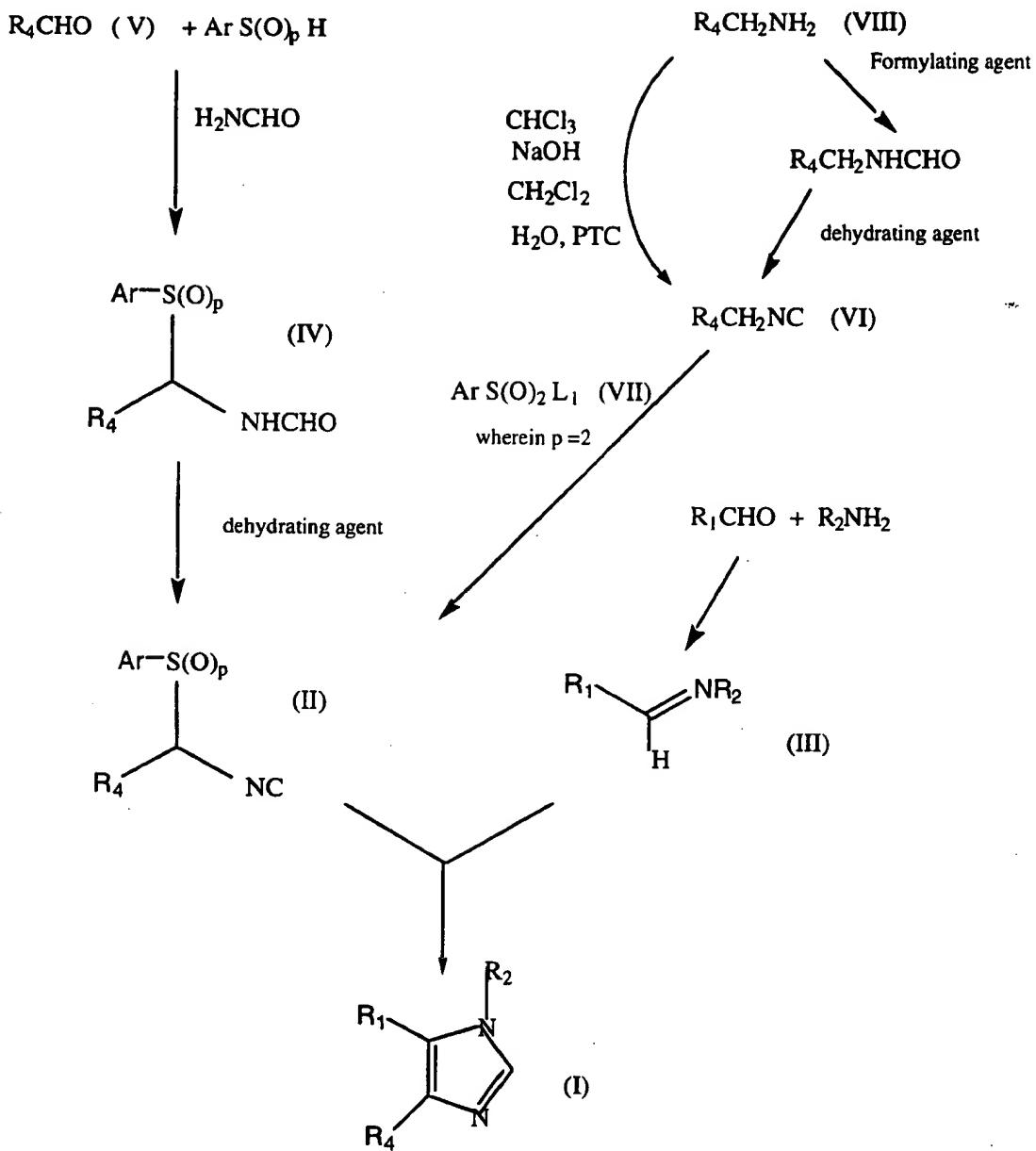
25 It is also noted that representative compounds of Formula (A) and (B) may be found in Table 1.

30 The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in Schemes I to XI herein. The synthesis provided for in these Schemes is applicable for the producing compounds of Formula (I) having a variety of different R₁, R₂, and R₄ groups which are reacted, employing optional substituents which are suitably protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. While the schemes describe 35 compounds of Formula (I) with Y as oxygen, one skilled in the art would readily be

able to make compounds of Formula (I) wherein Y is sulfur using similar reaction processes as exemplified herein.

Precursors of the groups R₁, R₂ and R₄ can be other R₁, R₂ and R₄ groups which can be interconverted by applying standard techniques for functional group interconversion. For example a compound of the formula (I) wherein R₂ is halo substituted C₁₋₁₀ alkyl can be converted to the corresponding C₁₋₁₀ alkylN₃ derivative by reacting with a suitable azide salt, and thereafter if desired can be reduced to the corresponding C₁₋₁₀alkylNH₂ compound, which in turn can be reacted with R₁₈S(0)₂X wherein X is halo (e.g., chloro) to yield the corresponding C₁₋₁₀alkylNHS(0)₂R₁₈ compound.

Alternatively a compound of the formula (I) where R₂ is halo-substituted C₁₋₁₀-alkyl can be reacted with an amine R₁₃R₁₄NH to yield the corresponding C₁₋₁₀-alkylNR₁₃R₁₄ compound, or can be reacted with an alkali metal salt of R₁₈SH to yield the corresponding C₁₋₁₀alkylSR₁₈ compound.

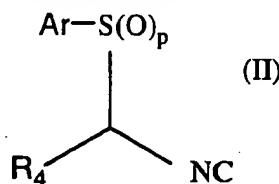


Scheme I, shown above, may be found in US patent 5,593,992, Adams et al., whose disclosure is incorporated by reference herein in its entirety. Compounds of 5 Formula (I) are suitably prepared by reacting a compound of the Formula (II), with a compound of the Formula (III) wherein p is 0 or 2, R_1 , R_2 and R_4 are as defined herein, for Formula (I), or are precursors of the groups R_1 , R_2 and R_4 , and Ar is an optionally substituted phenyl group, and thereafter if necessary converting a precursor of R_1 , R_2 and R_4 to a group R_1 , R_2 and R_4 . It is recognized that R_2NH_2 10 which is reacted with R_1CHO to form the imine, Formula (III) the R_2 moiety when it contains a reactive functional group, such as a primary or secondary amine, an

alcohol, or thiol compound the group must be suitably protected. Suitable protecting groups may be found in, Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981, whose disclosure is incorporated herein by reference. For instance, when R₂ is a heterocyclic ring, such as a piperidine ring, the 5 nitrogen is protected with groups such as t-Boc, CO₂R₁₈, or a substituted arylalkyl moiety.

Suitably, the reaction is performed at ambient temperature or with cooling (e.g. -50° to 10°) or heating in an inert solvent such as methylene chloride, DMF, tetrahydrofuran, toluene, acetonitrile, or dimethoxyethane in the presence of an 10 appropriate base such as K₂CO₃, t-buNH₂, 1,8-diazabicyclo [5.4.0.] undec-7-ene (DBU), or a guanidine base such as 1,5,7-triaza-bicyclo [4.4.0] dec-5-ene (TBD). The intermediates of formula (II) have been found to be very stable and capable of storage for a long time. Preferably, p is 2. PTC is defined as a phase transfer catalyst for use herein.

15 Compounds of the Formula (II) have the structure:



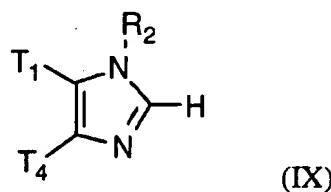
wherein p is 0, or 2; R₄ is as defined for Formula (I) and Ar is an optionally substituted aryl as defined herein. Suitably, Ar is phenyl optionally substituted by C₁₋₄alkyl, C₁₋₄alkoxy or halo. Preferably Ar is phenyl or 4-methylphenyl, i.e. a 20 tosyl derivative.

Reaction a compound of the Formula (II) wherein p = 2, with a compound of the Formula (III)-Scheme I gives consistently higher yields of compounds of Formula (I) than when p=0. In addition, the reaction of Formula (II) compounds wherein p = 2 is more environmentally and economically attractive. When p=0, the 25 preferred solvent used is methylene chloride, which is environmentally unattractive for large scale processing, and the preferred base, TBD, is also expensive, and produces some byproducts and impurities, than when using the commercially attractive synthesis (p=2) as further described herein.

As noted, Scheme I utilizes the 1,3-dipolar cycloadditions of an anion of a 30 substituted aryl thiomethylisocyanide (when p=0) to an imine. More specifically, this reaction requires a strong base, such as an amine base, to be used for the deprotonation step. The commercially available TBD is preferred although

t-butoxide, Li⁺ or Na⁺, or K⁺ hexamethyldisilazide may also be used. While methylene chloride is the preferred solvent, other halogenated solvents, such as chloroform or carbon tetrachloride; ethers, such as THF, DME, DMF, diethylether, t-butyl methyl ether; as well as acetonitrile, toluene or mixtures thereof can be utilized. The reaction may take place from about -20°C to about 40°C, preferably from about 0°C to about 23°C, more preferably from about 0°C to about 10°C, and most preferably about 4°C for reactions involving an R₁ group of pyrimidine. For compounds wherein R₁ is pyridine, it is recognized that varying the reations conditions of both temperature and solvent may be necessary, such as decreasing temperatures to about -50°C or changing the solvent to THF.

In a further process, compounds of Formula (I) may be prepared by coupling a suitable derivative of a compound of Formula (IX):



wherein T₁ is hydrogen and T₄ is R₄, or alternatively T₁ is R₁ and T₄ is H in which R₁, R₂ and R₄ are as hereinbefore defined; with: (i) when T₁ is hydrogen, a suitable derivative of the heteroaryl ring R₁H, under ring coupling conditions, to effect coupling of the heteroaryl ring R₁ to the imidazole nucleus at position 5; (ii) when T₄ is hydrogen, a suitable derivative of the aryl ring R₄H, under ring coupling conditions, to effect coupling of the aryl ring R₄ to the imidazole nucleus at position 4.

Such aryl/heteroaryl coupling reactions are well known to those skilled in the art. In general, an organometallic synthetic equivalent of an anion of one component is coupled with a reactive derivative of the second component, in the presence of a suitable catalyst. The anion equivalent may be formed from either the imidazole of Formula (IX), in which case the aryl/heteroaryl compound provides the reactive derivative, or the aryl/heteroaryl compound in which case the imidazole provides the reactive derivative. Accordingly, suitable derivatives of the compound of Formula (IX) or the aryl/heteroaryl rings include organometallic derivatives such as organomagnesium, organozinc, organostannane and boronic acid derivatives and suitable reactive derivatives include the bromo, iodo, fluorosulfonate and trifluoromethanesulphonate derivatives. Suitable procedures are described in WO 91/19497, the disclosure of which is incorporated by reference herein.

Suitable organomagnesium and organozinc derivatives of a compound of Formula (IX) may be reacted with a halogen, fluorosulfonate or triflate derivative of the heteroaryl or aryl ring, in the presence of a ring coupling catalyst, such as a palladium (0) or palladium (II) catalyst, following the procedure of Kumada *et al.*,

5 Tetrahedron Letters, 22, 5319 (1981). Suitable such catalysts include *tetrakis*-(triphenylphosphine)palladium and $PdCl_2[1,4\text{-}bis\text{-}(diphenylphosphino)\text{-}butane]}$, optionally in the presence of lithium chloride and a base, such as triethylamine. In addition, a nickel (II) catalyst, such as $Ni(II)Cl_2(1,2\text{-biphenylphosphino})ethane$, may also be used for coupling an aryl ring, following the procedure of Pridgen *et al.*, J.

10 Org. Chem, 1982, 47, 4319. Suitable reaction solvents include hexamethylphosphoramide. When the heteroaryl ring is 4-pyridyl, suitable derivatives include 4-bromo- and 4-iodo-pyridine and the fluorosulfonate and triflate esters of 4-hydroxy pyridine. Similarly, suitable derivatives for when the aryl ring is phenyl include the bromo, fluorosulfonate, triflate and, preferably, the iodo-derivatives. Suitable

15 20 organomagnesium and organozinc derivatives may be obtained by treating a compound of Formula (IX) or the bromo derivative thereof with an alkyl lithium compound to yield the corresponding lithium reagent by deprotonation or transmetallation, respectively. This lithium intermediate may then be treated with an excess of a magnesium halide or zinc halide to yield the corresponding organometallic reagent.

A trialkyltin derivative of the compound of Formula (IX) may be treated with a bromide, fluorosulfonate, triflate, or, preferably, iodide derivative of an aryl or heteroaryl ring compound, in an inert solvent such as tetrahydrofuran, preferably containing 10% hexamethylphosphoramide, in the presence of a suitable coupling catalyst, such as a palladium (0) catalyst, for instance *tetrakis*-(triphenylphosphine)-palladium, by the method described in by Stille, J. Amer. Chem. Soc, 1987, 109, 5478, US Patents 4,719,218 and 5,002,942, or by using a palladium (II) catalyst in the presence of lithium chloride optionally with an added base such as triethylamine, in an inert solvent such as dimethyl formamide. Trialkyltin derivatives may be conveniently obtained by metallation of the corresponding compound of Formula (IX) with a lithiating agent, such as *s*-butyl-lithium or *n*-butyllithium, in an ethereal solvent, such as tetrahydrofuran, or treatment of the bromo derivative of the corresponding compound of Formula (IX) with an alkyl lithium, followed, in each case, by treatment with a trialkyltin halide. Alternatively, the bromo- derivative of a compound of Formula (IX) may be treated with a suitable heteroaryl or aryl trialkyl

tin compound in the presence of a catalyst such as *tetrakis*-(triphenyl-phosphine)-palladium, under conditions similar to those described above.

Boronic acid derivatives are also useful. Hence, a suitable derivative of a compound of Formula (IX), such as the bromo, iodo, triflate or fluorosulphonate derivative, may be reacted with a heteroaryl- or aryl-boronic acid, in the presence of a palladium catalyst such as *tetrakis*-(triphenylphosphine)-palladium or $\text{PdCl}_2[\text{I},\text{4-bis-(diphenyl-phosphino)-butane}]$ in the presence of a base such as sodium bicarbonate, under reflux conditions, in a solvent such as dimethoxyethane (see Fischer and Haviniga, *Rec. Trav. Chim. Pays Bas*, **84**, 439, 1965, Snieckus, V., *Tetrahedron Lett.*, **29**, 2135, 1988 and Terashimia, M., *Chem. Pharm. Bull.*, **11**, 4755, 1985). Non-aqueous conditions, for instance, a solvent such as DMF, at a temperature of about 100°C, in the presence of a Pd(II) catalyst may also be employed (see Thompson W J *et al*, *J Org Chem*, **49**, 5237, 1984). Suitable boronic acid derivatives may be prepared by treating the magnesium or lithium derivative with a trialkylborate ester, such as triethyl, tri-*iso*-propyl or tributylborate, according to standard procedures.

In such coupling reactions, it will be readily appreciated that due regard must be exercised with respect to functional groups present in the compounds of Formula (IX). Thus, in general, amino and sulfur substituents should be non-oxidized or protected.

Compounds of Formula (IX) are imidazoles and may be obtained by any of the procedures herein before described for preparing compounds of Formula (I). In particular, an α -halo-ketone or other suitably activated ketones $\text{R}_4\text{COCH}_2\text{Hal}$ (for compounds of Formula (IX) in which T₁ is hydrogen) or $\text{R}_1\text{COCH}_2\text{Hal}$ (for compounds of Formula (IX) in which T₄ is hydrogen) may be reacted with an amidine of the formula $\text{R}_2\text{NH-C=NH}$, wherein R₂ is as defined in Formula (I), or a salt thereof, in an inert solvent such as a halogenated hydrocarbon solvent, for instance chloroform, at a moderately elevated temperature, and, if necessary, in the presence of a suitable condensation agent such as a base. The preparation of suitable α -halo-ketones is described in WO 91/19497. Suitable reactive esters include esters of strong organic acids such as a lower alkane sulphonic or aryl sulphonic acid, for instance, methane or *p*-toluene sulphonic acid. The amidine is preferably used as the salt, suitably the hydrochloride salt, which may then be converted into the free amidine *in situ*, by employing a two phase system in which the reactive ester is in an inert organic solvent such as chloroform, and the salt is in an aqueous phase to which a solution of an aqueous base is slowly added, in dimolar amount, with vigorous

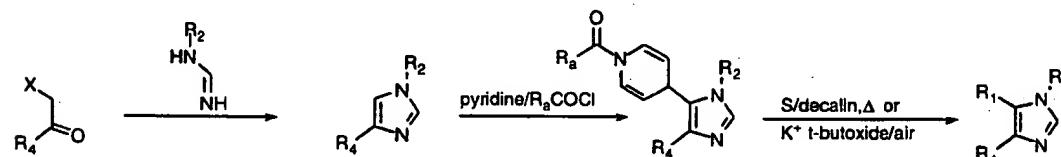
stirring. Suitable amidines may be obtained by standard methods, see for instance, Garigipati R, *Tetrahedron Letters*, 190, 31, 1989.

Compounds of Formula (I) may also be prepared by a process which comprises reacting a compound of Formula (IX), wherein T₁ is hydrogen, with an N-5 acyl heteroaryl salt, according to the method disclosed in US patent 4,803,279, US patent 4,719,218 and US patent 5,002,942, to give an intermediate in which the heteroaryl ring is attached to the imidazole nucleus and is present as a 1,4-dihydro derivative thereof, which intermediate may then be subjected to oxidative-deacylation conditions (Scheme II). The heteroaryl salt, for instance a pyridinium salt, may be either preformed or, more preferably, prepared *in situ* by adding a substituted carbonyl halide (such as an acyl halide, an aroyl halide, an arylalkyl haloformate ester, or, preferably, an alkyl haloformate ester, such as acetyl bromide, benzoylchloride, benzyl chloroformate, or, preferably, ethyl chloroformate) to a 10 solution of the compound of Formula (IX) in the heteroaryl compound R₁H or in an inert solvent such as methylene chloride to which the heteroaryl compound has been 15 added. Suitable deacylating and oxidizing conditions are described in U.S. Patent Nos. 4,803,279, 4,719,218 and 5,002,942, which references are hereby incorporated by reference in their entirety. Suitable oxidizing systems include sulfur in an inert solvent or solvent mixture, such as decalin, decalin and diglyme, *p*-cymene, xylene or mesitylene, under reflux conditions, or, preferably, potassium *t*-butoxide in *t*-butanol with dry air or oxygen.

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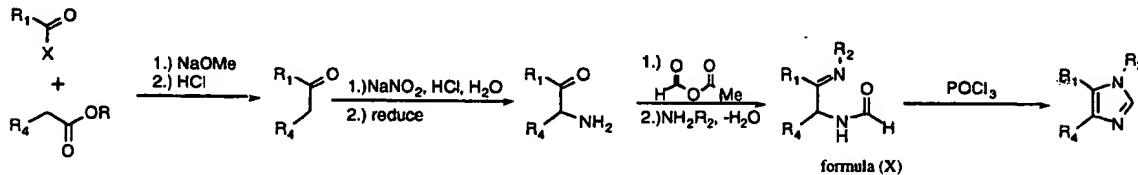
Scheme II

In a further process, illustrated in Scheme III below, compounds of Formula (I) may be prepared by treating a compound of Formula (X) thermally or with the aid of a cyclising agent such as phosphorus oxychloride or phosphorus pentachloride 30 (see Engel and Steglich, *Liebigs Ann Chem*, 1978, 1916 and Strzybny *et al.*, *J Org Chem*, 1963, 28, 3381). Compounds of Formula (X) may be obtained, for instance, by acylating the corresponding α -keto-amine with an activated formate derivative such as the corresponding anhydride, under standard acylating conditions followed



by formation of the imine with R_2NH_2 . The aminoketone may be derived from the parent ketone by oxamination and reduction and the requisite ketone may in turn be prepared by decarboxylation of the beta-ketoester obtained from the condensation of an aryl (heteroaryl) acetic ester with the R_1COX component.

5

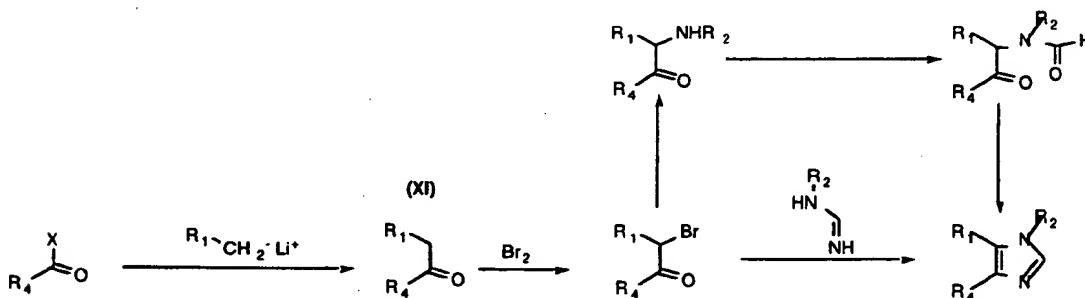


Scheme III

In Scheme IV illustrated below, two (2) different routes which use ketone (formula XI) for preparing a compound of Formula (I). A heterocyclic ketone (XI) is prepared by adding the anion of the alkyl heterocycle such as 4-methyl-quinoline (prepared by treatment thereof with an alkyl lithium, such as *n*-butyl lithium) to an N-alkyl-O-alkoxybenzamide, ester, or any other suitably activated derivative of the same oxidation state. Alternatively, the anion may be condensed with a benzaldehyde, to give an alcohol which is then oxidized to the ketone (XI).

10 (formula XI) for preparing a compound of Formula (I). A heterocyclic ketone (XI) is prepared by adding the anion of the alkyl heterocycle such as 4-methyl-quinoline (prepared by treatment thereof with an alkyl lithium, such as *n*-butyl lithium) to an N-alkyl-O-alkoxybenzamide, ester, or any other suitably activated derivative of the same oxidation state. Alternatively, the anion may be condensed with a

15 benzaldehyde, to give an alcohol which is then oxidized to the ketone (XI).



Scheme IV

20

In a further process, N-substituted compounds of Formula (I) may be prepared by treating the anion of an amide of Formula (XII):



wherein R_1 and R_2 with:

25 (a) a nitrile of the Formula (XIII):

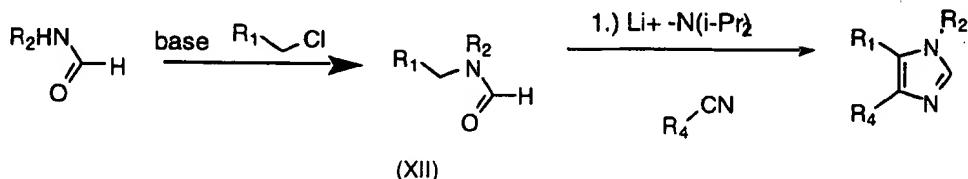


wherein R_4 is as hereinbefore defined, or

(b) an excess of an acyl halide, for instance an acyl chloride, of the Formula (XIV):



wherein R_4 is as hereinbefore defined and Hal is halogen, or a corresponding anhydride, to give a *bis*-acylated intermediate which is then treated with a source of ammonia, such as ammonium acetate.

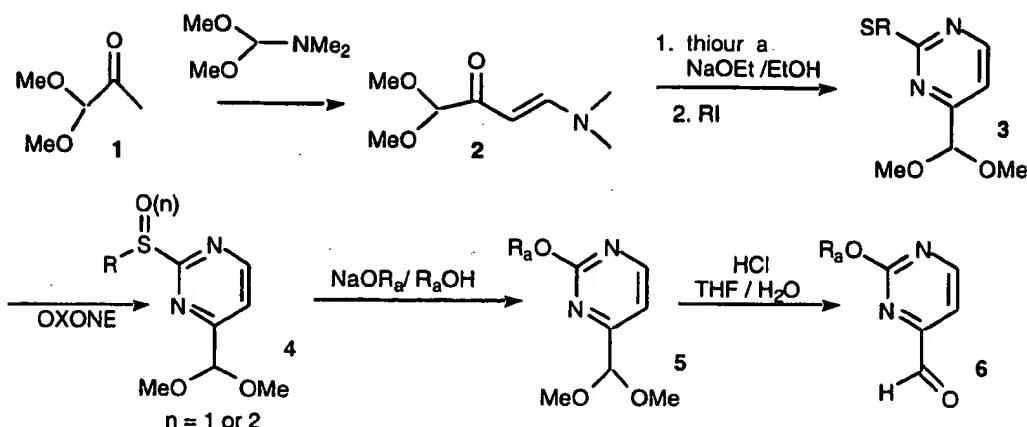


Scheme V

10

One variation of this approach is illustrated in Scheme V above. A primary amine (R_2NH_2) is treated with a halomethyl heterocycle of Formula $\text{R}_1\text{CH}_2\text{X}$ to give the secondary amine which is then converted to the amide by standard techniques. Alternatively the amide may be prepared as illustrated in scheme V by alkylation of the formamide with $\text{R}_1\text{CH}_2\text{X}$. Deprotonation of this amide with a strong amide base, such as lithium di-*iso*-propyl amide or sodium *bis*-(trimethylsilyl)amide, followed by addition of an excess of an aryl chloride yields the *bis*-acylated compound which is then closed to an imidazole compound of Formula (I), by heating in acetic acid containing ammonium acetate. Alternatively, 15 the anion of the amide may be reacted with a substituted aryl nitrile to produce the imidazole of Formula (I) directly.

20 The following description and schemes are further exemplification of the process as previously described above in Scheme I. Various pyrimidine aldehyde derivatives 6, as depicted in scheme VI below, can be prepared by modification of the procedures of Bredereck et al. (*Chem. Ber.* 1964, 97, 3407) whose disclosure is incorporated by reference herein. These pyrimidine aldehydes are then utilized as 25 intermediates in the synthesis as further described herein.



Scheme VI

The reaction of imines with tosylmethyl isocyanides was first reported by van 5 Leusen (van Leusen, et al., *J. Org. Chem.* 1977, 42, 1153.) Reported were the following conditions: tert butyl amine (*t*BuNH₂) in dimethoxyethane (DME), K₂CO₃ in MeOH, and NaH in DME. Upon re-examination of these conditions each was found to produce low yields. A second pathway involving amine exchange to produce the *t*-butyl imine followed by reaction with the isocyanide to produce a 1- 10 *t*Bu imidazole was also operating. This will likely occur using any primary amine as a base. The secondary amines, while not preferred may be used, but may also decompose the isocyanide slowly. Reactions will likely require about 3 equivalents of amine to go to completion, resulting in approximately 50% isolated yields. Hindered 15 secondary amines (diisopropylamine) while usable are very slow and generally not too effective. Use of tertiary and aromatic amines, such as pyridine, and triethylamine gave no reaction under certain test conditions, but more basic types such as DBU, and 4-dimethylamino pyridine (DMAP) while slow, did produce some yields and hence may be suitable for use herein.

As depicted in Schemes VII and VIII below, the pyrimidine aldehydes of 20 Scheme VI, can be condensed with a primary amine, to generate an imine, which may suitably be isolated or reacted in situ, with the desired isocyanide in the presence of a variety of suitable bases, and solvents as described herein to afford the 5-(4-pyrimidinyl)-substituted imidazoles, wherein R₂ and R₄ are as defined herein for Formula (I) compounds.

25 One preferred method for preparing compounds of Formula (I) is shown below in Scheme VII. The imines, prepared and isolated in a separate step were often tars, which were hard to handle. The black color was also often carried over

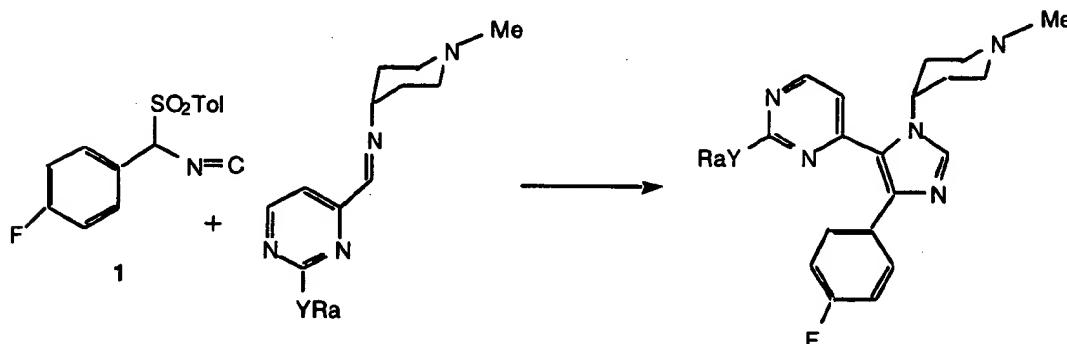
into the final product. The yield for making the imines varied, and environmentally less-acceptable solvents, such as CH_2Cl_2 were often used in their preparation.

This reaction, wherein $p=2$, requires a suitable base for the reaction to proceed. The reaction requires a base strong enough to deprotonate the isonitrile.

5 Suitable bases include an amine, a carbonate, a hydride, or an alkyl or aryl lithium reagent; or mixtures thereof. Bases include, but are not limited to, potassium carbonate, sodium carbonate, primary and secondary amines, such as t-butylamine, diisopropyl amine, morpholine, piperidine, pyrrolidine, and other non-nucleophilic bases, such as DBU, DMAP and 1,4-diazabicyclo[2.2.2]octane (DABCO).

10 Suitable solvents for use herein, include but are not limited to N,N-dimethyl-formamide (DMF), MeCN, halogenated solvents, such as methylene chloride or chloroform, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), alcohols, such as methanol or ethanol, benzene, or toluene, DME or EtOAc. Preferably the solvent is DMF, DME, THF, or MeCN, more preferably DMF. Product isolation may

15 generally be accomplished by adding water and filtering the product as a clean compound.



20

SchemeVII

While not convenient for large scale work, addition of NaH to the isonitrile, perhaps with temperatures lower than 25 °C (in THF) are likely needed. Additionally, BuLi has also been reported to be an effective base for deprotonating tosyl benzylisonitriles at -50 °C. (DiSanto, et al., *Synth. Commun.* 1995, 25, 795).

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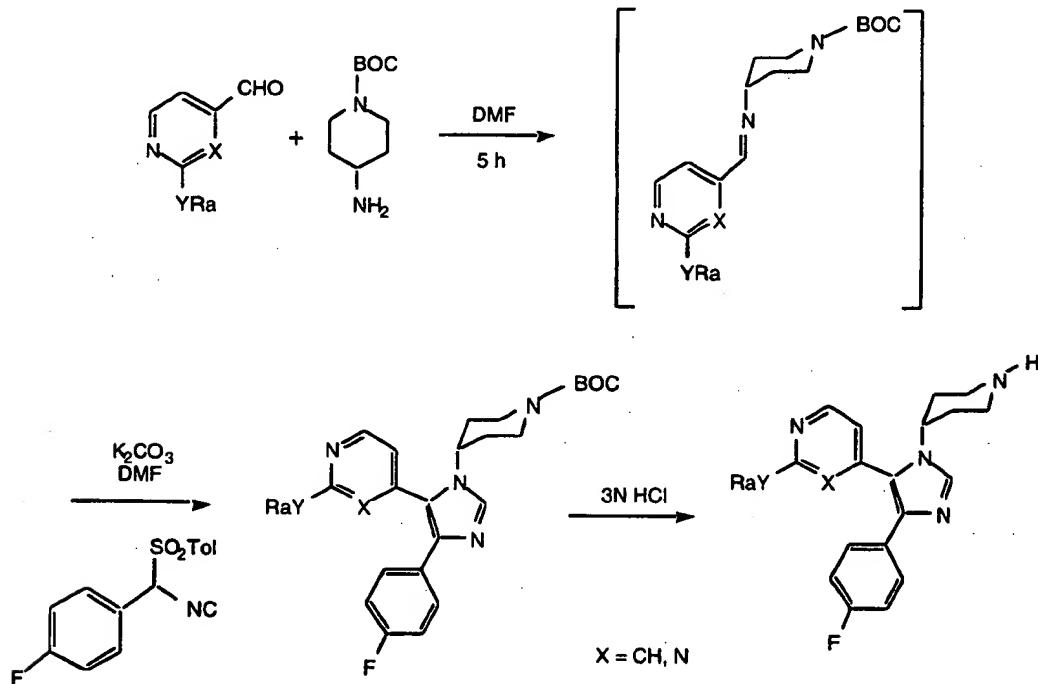
Various temperature conditions may be utilized depending upon the preferred base. For instance, tBuNH₂/DME, K₂CO₃/MeOH, K₂CO₃ in DMF, at temperatures above 40 °C, the yields may drop to about 20% but little difference is expected between 0°C and 25 °C. Consequently, temperature ranges below 0°C, and above 80°C are contemplated as also being within the scope of this invention.

30

Preferably, the temperature ranges are from about 0°C to about 25°C. For purposes

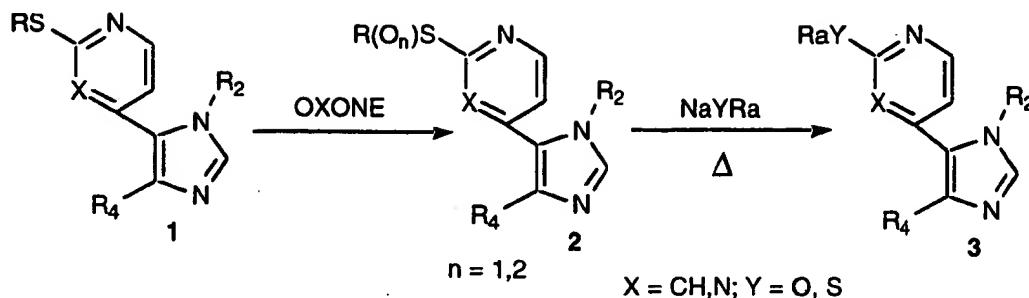
herein, room temperature, is generally depicted as 25°C, but it is recognized that this may vary from 20°C to 30°C.

As shown in Scheme VIII below, the imine is preferably formed *in situ* in a solvent. This preferred synthesis, is a process which occurs as a one-pot synthesis. Suitably, when the primary amine is utilized as a salt, such as in the dihydrochloride salt in the Examples, the reaction may further include a base, such as potassium carbonate prior to the addition of the isonitrile. Alternatively, the piperidine nitrogen may be required to be protected (PG) as shown below, suitably the PG is BOC or $C(O)_2R$, wherein R is preferably alkyl, aryl, arylalkyl moieties well known to those skilled in the art. Reaction conditions, such as solvents, bases, temperatures, etc. are similar to those illustrated and discussed above for the isolated imine as shown in Scheme VII. One skilled in the art would readily recognize that under some circumstances, the *in situ* formation of the imine may require dehydrating conditions, or may require acid catalysis.



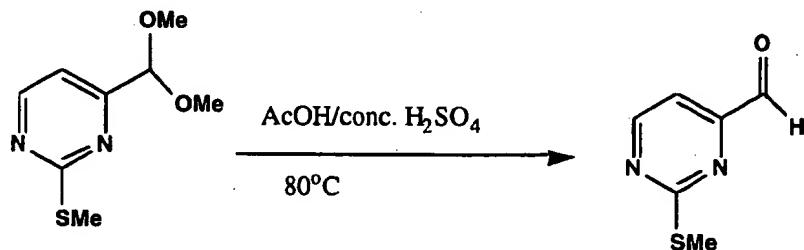
Scheme VIII

20 Scheme IX, describes an alternative process for making compounds of formula (I). In this particular instance, the alkylthio moiety is oxidized to the methyl sulfinyl or sulfonyl moiety which is reacted with a suitable YR_a moiety.



Scheme IX

Another embodiment of the present invention is the novel hydrolysis of 2-thiomethylpyrimidine acetal to 2-thiomethylpyrimidine aldehyde, as shown in Scheme X below. Hydrolysis of the acetal to aldehyde using various known reaction conditions, such as formic acid, did not produce a satisfactory yield of the aldehyde, (<13%) was obtained. The preferred synthesis involves the use of AcOH (fresh) as solvent and concentrated H₂SO₄ under heating conditions, preferably a catalytic amount of sulfuric acid. Heating conditions include temperatures from about 60 to 85°C, preferably from about 70 to about 80°C as higher temperatures show a darkening of the reaction mixture. After the reaction is completed the mixture is cooled to about room temperature and the acetic acid is removed. A more preferred alternative procedure to this involves heating the acetal in 3N HCl at 40°C for about 18 hours, cooling and extracting the bicarbonate neutralized solution into EtOAc.



Scheme X

The final 2-(RaY)pyrimidin-4-yl imidazole compounds of Formula (I), as well as similar pyridine containing compounds can be prepared by one of three methods: 1) direct reaction of the 2-(RaY)pyrimidine imine with the isonitrile; 2) oxidation of the 2-alkylthiopyrimidine derivative to the corresponding sulfoxide followed by displacement with the desired HYRa under basic conditions, for example using a metal salt of HYRa or in the presence of a non-nucleophilic amine or alkali metal base; or 3) reaction of the 2-halopyrimidine or pyridine imine with the isonitrile followed by displacement with HYRa under basic conditions described in

the second method, see also Adams et al., USSN 08/659,102 filed 3 June 1996, Scheme XI, whose disclosure is incorporated herein by reference in its entirety.

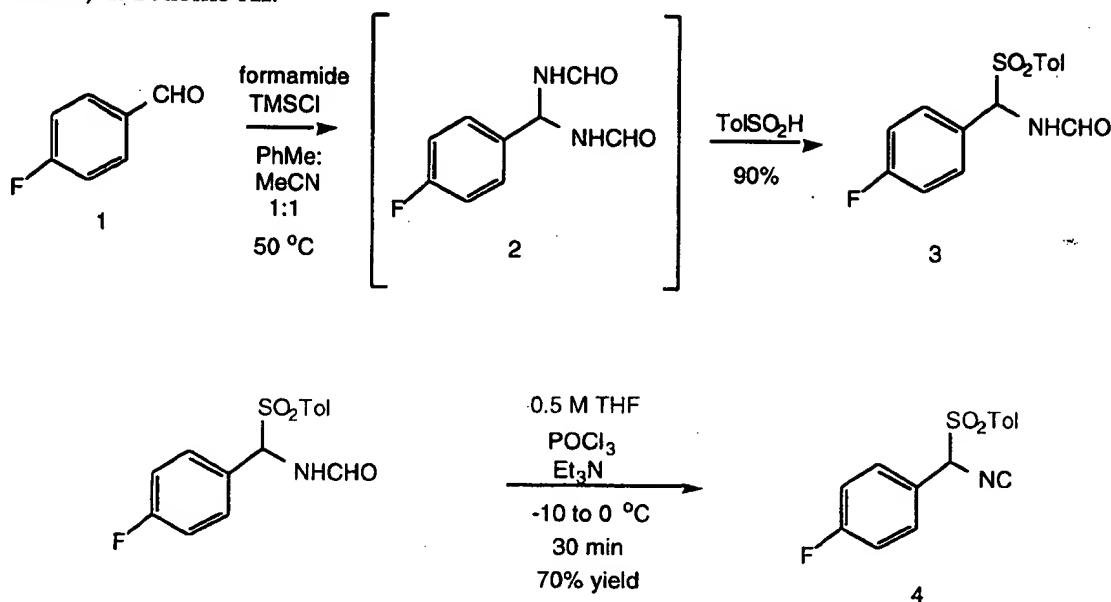
While these schemes herein are presented, for instance, with an optionally substituted piperidine moiety for the resultant R₂ position, or a 4-fluoro phenyl for R₄, any suitable R₂ moiety or R₄ moiety may be added in this manner if it can be prepared on the primary amine. Similarly, any suitable R₄ can be added via the isonitrile route.

The compounds of Formula (II), in Scheme I, may be prepared by the methods of van Leusen et al., *supra*. For example a compound of the Formula (II) may be prepared by dehydrating a compound of the Formula (IV)-Scheme I, wherein Ar, R₄ and p are as defined herein.

Suitable dehydrating agents include phosphorus oxychloride, oxalyl chloride, thionyl chloride, phosgene, or tosyl chloride in the presence of a suitable base such as triethylamine or diisopropylethylamine, or similar bases, etc. such as pyridine. Suitable solvents are dimethoxy ether, tetrahydrofuran, or halogenated solvents, preferably THF. The reaction is most efficient when the reaction temperatures are kept between -10°C and 0°C. At lower temperatures incomplete reaction occurs and at higher temperatures, the solution turns dark and the product yield drops.

The compounds of formula (IV)-Scheme I may be prepared by reacting a compound of the formula (V)-Scheme I, R₄CHO where R₄ is as defined herein, with ArS(0)_pH and formamide with or without water removal, preferably under dehydrating conditions, at ambient or elevated temperature e.g. 30° to 150°, conveniently at reflux, optionally in the presence of an acid catalyst. Alternatively trimethylsilylchloride can be used in place of the acid catalyst. Examples of acid catalysts include camphor-10-sulphonic acid, formic acid, p-toluenesulphonic acid, hydrogen chloride or sulphuric acid.

An optimal method of making an isonitrile of Formula (II) is illustrated below, in Scheme XI.



5

SCHEME XI

The conversion of the substituted aldehyde to the tosylbenzyl formamide may be accomplished by heating the aldehyde, 1-Scheme XI, with an acid, such as p-toluene-sulfonic acid, formic acid or camphorsulfonic acid; with formamide and p-toluene-sulfinic acid [under reaction conditions of about 60°C for about 24 hours].

10 Preferably, no solvent is used. The reaction, may give poor yields (< 30%) when solvents, such as DMF, DMSO, toluene, acetonitrile, or excess formamide are used. Temperatures less than 60°C are generally poor at producing the desired product, and temperatures in excess of 60°C may produce a product which decomposes, or obtain a benzylic bis-formamide, 2-Scheme XI.

15 Another embodiment of the present invention is the synthesis of the tosyl benzyl formamide compound, achieved by reacting the bisformamide intermediate, 2-Scheme XI with p-toluenesulfinic acid. In this preferred route, preparation of the bis-formamide from the aldehyde is accomplished by heating the aldehyde with formamide, in a suitable solvent with acid catalysis. Suitable solvents are toluene, acetonitrile, DMF, and DMSO or mixtures thereof. Acid catalysts, are those well known in the art, and include but are not limited to hydrogen chloride, p-toluenesulfonic acid, camphorsulfonic acid, and other anhydrous acids. The reaction can be conducted at temperatures ranging from about 25°C to 110°C, preferably about 50°C, suitably for about 4 to about 5 hours, longer reaction times are also acceptable. Product decomposition and lower yields may be observed at

higher temperatures (>70°C) at prolonged reaction times. Complete conversion of the product generally requires water removal from the reaction mixture.

Preferred conditions for converting a bis-formamide derivative to the tosyl benzyl formamide are accomplished by heating the bisformamide in a suitable 5 solvent with an acid catalyst and p-toluenesulfinic acid. Solvents for use in this reaction include but are not limited to toluene, and acetonitrile or mixtures thereof. Additional mixtures of these solvents with DMF, or DMSO may also be used but may result in lower yields. Temperatures may range from about 30°C to about 100°C. Temperatures lower than 40°C and higher than 60°C are not preferred as the 10 yield and rate decreases. Preferably the range is from about 40 to 60°C, most preferably about 50°C. The optimal time is about 4 to 5 hours, although it may be longer. Preferably, acids used include but are not limited to, toluenesulfonic acid, camphorsulfonic acid, and hydrogen chloride and other anhydrous acids. Most 15 preferably the bisformamide is heated in toluene:acetonitrile in a 1:1 ratio, with p-toluenesulfinic acid and hydrogen chloride.

Another embodiment of the present invention is the preferred synthetic route for synthesis of the tosylbenzyl formamide compound which is accomplished using a one-pot procedure. This process first converts the aldehyde to the bis-formamide derivative and subsequently reacts the bis-formamide derivative with toluenesulfinic 20 acid. This procedure combines the optimized conditions into a single, efficient process. High yields, >90% of the aryl benzylformamide may be obtained in such a manner.

Preferred reaction conditions employ a catalyst, such as trimethylsilyl 25 chloride (TMSCl), in a preferred solvent, toluene:acetonitrile, preferably in a 1:1 ratio. A reagent, such as TMSCl, is preferred which reacts with water produced therein and at the same time produces hydrogen chloride to catalyze the reaction. Also preferred is use of hydrogen chloride and p-toluenesulfonic acid. Therefore, three suitable reaction conditions for use herein include 1) use of a dehydrating agent 30 which also provides hydrogen chloride, such as TMSCl; or by 2) use of a suitable dehydrating agent and a suitable source of acid source, such as but not limited to, camphorsulfonic acid, hydrogen chloride or toluenesulfonic acid; and 3) alternative dehydrating conditions, such as the azeotropic removal of water, and using an acid catalyst and p-toluene sulfinic acid.

Compounds of the formula (II) where p is 2 may also be prepared by reacting 35 in the presence of a strong base a compound of the formula (VI) -Scheme I, R_4CH_2NC with a compound of the formula (VII)-Scheme I, $ArSO_2L_1$ wherein R_4

and Ar are as defined herein and L₁ is a leaving group such as halo, e.g. fluoro. Suitable strong bases include, but are not limited to, alkyl lithiums such as butyl lithium or lithium diisopropylamide (Van Leusen *et al.*, *Tetrahedron Letters*, No. 23, 2367-68 (1972)).

5 The compounds of formula (VI)-Scheme I may be prepared by reacting a compound of the formula (VIII)-Scheme I, R₄CH₂NH₂ with an alkyl formate (e.g. ethylformate) to yield an intermediate amide which can be converted to the desired isonitrile by reacting with well known dehydrating agent, such as but not limited to oxalyl chloride, phosphorus oxychloride or tosyl chloride in the presence of a
10 suitable base such as triethylamine.

Alternatively a compound of the formula (VIII) - Scheme I may be converted to a compound of the formula (VI)- Scheme I by reaction with chloroform and sodium hydroxide in aqueous dichloromethane under phase transfer catalysis.

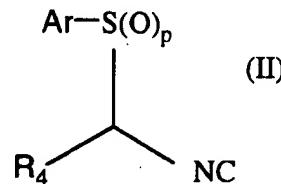
15 The compounds of the formula (III) - Scheme I may be prepared by reacting a compound of the formula R₁CHO with a primary amine R₂NH₂.

The amino compounds of the formula (VIII) - Scheme I are known or can be prepared from the corresponding alcohols, oximes or amides using standard functional group interconversions.

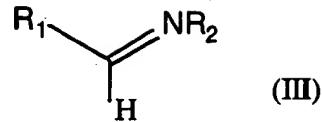
20 Suitable protecting groups for use with hydroxyl groups and the imidazole nitrogen are well known in the art and described in many references, for instance, Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981. Suitable examples of hydroxyl protecting groups include silyl ethers, such as t-butyldimethyl or t-butyldiphenyl, and alkyl ethers, such as methyl connected by an alkyl chain of variable link, (CR₁₀R₂₀)_n. Suitable examples of
25 imidazole nitrogen protecting groups include tetrahydropyranyl.

Pharmaceutically acid addition salts of compounds of Formula (I) may be obtained in known manner, for example by treatment thereof with an appropriate amount of acid in the presence of a suitable solvent.

30 The present invention also related to a process for preparing a compound of Formula (I) which process comprises reacting a compound of the Formula (II) :



with a compound of the Formula (III):



wherein p is 0 or 2; and a base strong enough to deprotonate the isonitrile moiety of
 5 Formula (II); and R₁, R₂ and R₄ are as defined in Formula (I), or are precursors of the groups R₁, R₂ and R₄ and Ar is an optionally substituted phenyl group, and thereafter if necessary, converting a precursor of R₁, R₂ and R₄ to a group R₁, R₂ and R₄.

One preferred reaction condition includes p=0, and TBD as a base.

Other preferred reaction conditions include p=2, the base is an amine, a carbonate, a
 10 hydride, or an alkyl or aryl lithium reagent.

Preferably, the imine of Formula (III), is isolated prior to reaction with Formula (II).

More preferably, the imine of Formula (III), is formed in situ prior to reaction with
 Formula (II).

Preferably, the imine is formed in situ by reacting an aldehyde of the formula
 15 R₁CHO, wherein R₁ is as defined for Formula (I), with a primary amine of the formula R₂NH₂, wherein R₂ is as defined for Formula (I).

More preferably, formation of the imine in situ utilizes dehydrating conditions, and preferred solvents are N,N-dimethyl-formamide (DMF), halogenated solvents, tetrahydrofuran (THF), dimethylsulfoxide (DMSO), alcohols, benzene, or toluene, or DME.

20 Preferably, the primary amine R₂NH₂ for use herein is where R₂ is piperidine, 1-Formyl-4-piperidine, 1-benzyl-4-piperidine, 1-methyl-4-piperidine, 1-ethoxycarbonyl-4-piperidine, 2,2,6,6-tetramethyl-4-piperidine, morpholino ethyl, morpholino propyl, pyrrolidinyl propyl, or piperidinyl propyl.

25 METHODS OF TREATMENT

For purposes herein, use of the term "compound of Formula (I)" is representative not only of compounds of Formula (I) but also compounds of Formula (A) and Formula (B), unless specifically indicated otherwise.

30 The compounds of Formula (I) or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated cytokine production by such mammal's cell, such as but not limited to monocytes and/or macrophages.

Compounds of Formula (I) are capable of inhibiting proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF and are therefore of use in therapy. IL-1, IL-6, IL-8 and TNF affect a wide variety of cells and tissues and these cytokines, as well as other leukocyte-derived cytokines, are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these pro-inflammatory cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering an effective cytokine-interfering 10 amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Compounds of Formula (I) are capable of inhibiting inducible proinflammatory proteins, such as COX-2, also referred to by many other names such as prostaglandin endoperoxide synthase-2 (PGHS-2) and are therefore of use in therapy. These proinflammatory lipid mediators of the cyclooxygenase (CO) 15 pathway are produced by the inducible COX-2 enzyme. Regulation, therefore of COX-2 which is responsible for the these products derived from arachidonic acid, such as prostaglandins affect a wide variety of cells and tissues are important and critical inflammatory mediators of a wide variety of disease states and conditions. Expression of COX-1 is not effected by compounds of Formula (I). This selective 20 inhibition of COX-2 may alleviate or spare ulcerogenic liability associated with inhibition of COX-1 thereby inhibiting prostoglandins essential for cytoprotective effects. Thus inhibition of these pro-inflammatory mediators is of benefit in controlling, reducing and alleviating many of these disease states. Most notably these inflammatory mediators, in particular prostaglandins, have been implicated in 25 pain, such as in the sensitization of pain receptors, or edema. This aspect of pain management therefore includes treatment of neuromuscular pain, headache, cancer pain, and arthritis pain. Compounds of Formula (I) or a pharmaceutically acceptable salt thereof, are of use in the prophylaxis or therapy in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

Accordingly, the present invention provides a method of inhibiting the 30 synthesis of COX-2 which comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The present invention also provides for a method of prophylaxis treatment in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

In particular, compounds of Formula (I) or a pharmaceutically acceptable salt 35 thereof are of use in the prophylaxis or therapy of any disease state in a human, or

other mammal, which is exacerbated by or caused by excessive or unregulated IL-1, IL-8 or TNF production by such mammal's cell, such as, but not limited to, monocytes and/or macrophages.

Accordingly, in another aspect, this invention relates to a method of

5 inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include

10 rheumatoid arthritis, osteoarthritis, stroke, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, multiple sclerosis, cachexia, bone resorption, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic

15 arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes, pancreatic β cells and Alzheimer's disease.

In a further aspect, this invention relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to

20 said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult

25 respiratory distress syndrome, stroke, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency

30 syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

Compounds of Formula (I) are also useful in the treatment of viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. The viruses contemplated for treatment herein are those that

35 produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibiting-compounds

of Formula (1). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as but not limited to, Herpes Zoster and Herpes Simplex. Accordingly, in a further aspect, this invention relates to a method of treating a mammal afflicted with 5 a human immunodeficiency virus (HIV) which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than in humans, in need of inhibition of TNF 10 production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to, lentivirus infections such as, equine infectious anaemia virus, caprine arthritis virus, visna virus, or maedi virus or retrovirus infections, such as but not limited to feline 15 immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus or other retroviral infections.

The compounds of Formula (I) may also be used topically in the treatment or prophylaxis of topical disease states mediated by or exacerbated by excessive 20 cytokine production, such as by IL-1 or TNF respectively, such as inflamed joints, eczema, psoriasis and other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

Compounds of Formula (I) have also been shown to inhibit the production of IL-8 (Interleukin-8, NAP). Accordingly, in a further aspect, this invention relates to 25 a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

There are many disease states in which excessive or unregulated IL-8 30 production is implicated in exacerbating and/or causing the disease. These diseases are characterized by massive neutrophil infiltration such as, psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. All of these diseases are associated with increased IL-8 production which is responsible for the chemotaxis of neutrophils into the inflammatory site. In contrast to other inflammatory cytokines 35 (IL-1, TNF, and IL-6), IL-8 has the unique property of promoting neutrophil

chemotaxis and activation. Therefore, the inhibition of IL-8 production would lead to a direct reduction in the neutrophil infiltration.

The compounds of Formula (I) are administered in an amount sufficient to inhibit cytokine, in particular IL-1, IL-6, IL-8 or TNF, production such that it is 5 regulated down to normal levels, or in some case to subnormal levels, so as to ameliorate or prevent the disease state. Abnormal levels of IL-1, IL-6, IL-8 or TNF, for instance in the context of the present invention, constitute: (i) levels of free (not cell bound) IL-1, IL-6, IL-8 or TNF greater than or equal to 1 picogram per ml; (ii) any cell associated IL-1, IL-6, IL-8 or TNF; or (iii) the presence of IL-1, IL-6, IL-8 10 or TNF mRNA above basal levels in cells or tissues in which IL-1, IL-6, IL-8 or TNF, respectively, is produced.

The discovery that the compounds of Formula (I) are inhibitors of cytokines, specifically IL-1, IL-6, IL-8 and TNF is based upon the effects of the compounds of Formulas (I) on the production of the IL-1, IL-8 and TNF in *in vitro* assays which 15 are described herein.

As used herein, the term "inhibiting the production of IL-1 (IL-6, IL-8 or TNF)" refers to:

- a) a decrease of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels by inhibition of the *in vivo* release 20 of the cytokine by all cells, including but not limited to monocytes or macrophages;
- b) a down regulation, at the genomic level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels;
- c) a down regulation, by inhibition of the direct synthesis of the cytokine (IL-1, IL-6, IL-8 or TNF) as a posttranslational event; or
- 25 d) a down regulation, at the translational level, of excessive *in vivo* levels of the cytokine (IL-1, IL-6, IL-8 or TNF) in a human to normal or sub-normal levels.

As used herein, the term "TNF mediated disease or disease state" refers to any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be released, such as but not limited to 30 IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF.

As used herein, the term "cytokine" refers to any secreted polypeptide that 35 affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce

them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, 5 epidermal keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF- α) and Tumor Necrosis Factor beta (TNF- β).

As used herein, the term "cytokine interfering" or "cytokine suppressive 10 amount" refers to an effective amount of a compound of Formula (I) which will cause a decrease in the *in vivo* levels of the cytokine to normal or sub-normal levels, when given to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production.

As used herein, the cytokine referred to in the phrase "inhibition of a 15 cytokine, for use in the treatment of a HIV-infected human" is a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration.

20 As TNF- β (also known as lymphotoxin) has close structural homology with TNF- α (also known as cachectin) and since each induces similar biologic responses and binds to the same cellular receptor, both TNF- α and TNF- β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

25 A new member of the MAP kinase family, alternatively termed CSBP, p38, or RK, has been identified independently by several laboratories recently. Activation of this novel protein kinase via dual phosphorylation has been observed in different cell systems upon stimulation by a wide spectrum of stimuli, such as physicochemical stress and treatment with lipopolysaccharide or proinflammatory 30 cytokines such as interleukin-1 and tumor necrosis factor. The cytokine biosynthesis inhibitors, of the present invention, compounds of Formula (I) have been determined to be potent and selective inhibitors of CSBP/p38/RK kinase activity. These inhibitors are of aid in determining the signaling pathways involvement in inflammatory responses. In particular, for the first time a definitive signal 35 transduction pathway can be prescribed to the action of lipopolysaccharide in cytokine production in macrophages. In addition to those diseases already noted,

treatment of stroke, neurotrauma, cardiac and renal reperfusion injury, congestive heart failure, chronic renal failure, angiogenesis & related processes, such as cancer, thrombosis, glomerulonephritis, diabetes and pancreatic β cells, multiple sclerosis, muscle degeneration, eczema, psoriasis, sunburn, and conjunctivitis are also included.

The cytokine inhibitors were subsequently tested in a number of animal models for anti-inflammatory activity. Model systems were chosen that were relatively insensitive to cyclooxygenase inhibitors in order to reveal the unique activities of cytokine suppressive agents. The inhibitors exhibited significant activity in many such *in vivo* studies. Most notable are its effectiveness in the collagen-induced arthritis model and inhibition of TNF production in the endotoxic shock model. In the latter study, the reduction in plasma level of TNF correlated with survival and protection from endotoxic shock related mortality. Also of great importance are the compounds effectiveness in inhibiting bone resorption in a rat fetal long bone organ culture system. Griswold et al., (1988) *Arthritis Rheum.* 31:1406-1412; Badger, et al., (1989) *Circ. Shock* 27, 51-61; Votta et al., (1994) *in vitro. Bone* 15, 533-538; Lee et al., (1993). *B Ann. N. Y. Acad. Sci.* 696, 149-170.

Chronic diseases which have an inappropriate angiogenic component are various ocular neovascularizations, such as diabetic retinopathy and macular degeneration. Other chronic diseases which have an excessive or increased proliferation of vasculature are tumor growth and metastasis, atherosclerosis, and certain arthritic conditions. Therefore CSBP kinase inhibitors will be of utility in the blocking of the angiogenic component of these disease states.

The term "excessive or increased proliferation of vasculature inappropriate angiogenesis" as used herein includes, but is not limited to, diseases which are characterized by hemangiomas and ocular diseases.

The term "inappropriate angiogenesis" as used herein includes, but is not limited to, diseases which are characterized by vesicle proliferation with accompanying tissue proliferation, such as occurs in cancer, metastasis, arthritis and atherosclerosis.

Accordingly, the present invention provides a method of treating a CSBP kinase mediated disease in a mammal in need thereof, preferably a human, which comprises administering to said mammal, an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical

composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent.

5 Compounds of Formula (I), pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of Formula (I) may be administered in conventional dosage forms prepared by combining a compound of

10 Formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of Formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be

15 appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

20 The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

25

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. to about 1g. When

30 a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

Compounds of Formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of Formula (I)

35 externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly

enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the formulation.

10 Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may 15 also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

10 Creams, ointments or pastes according to the present invention are semi-solid Formulations of the active ingredient for external application. They may be made by 20 mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or 25 its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The Formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, 30 and other ingredients such as lanolin, may also be included.

15 Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active 35 agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining

at 98-100°C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and 5 chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Compounds of Formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of 10 parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. Compounds of Formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol Formulation or a metered dose inhaler, may be prepared by conventional 15 techniques.

For all methods of use disclosed herein for the compounds of Formula (I), the daily oral dosage regimen will preferably be from about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to 30 mg/kg, more preferably from about 0.5 mg to 15mg. The daily parenteral dosage regimen about 0.1 to about 80 20 mg/kg of total body weight, preferably from about 0.2 to about 30 mg/kg, and more preferably from about 0.5 mg to 15mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in 25 the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill 30 in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The novel compounds of Formula (I) may also be used in association with 35 the veterinary treatment of mammals, other than humans, in need of inhibition of cytokine inhibition or production. In particular, cytokine mediated diseases for

treatment, therapeutically or prophylactically, in animals include disease states such as those noted herein in the Methods of Treatment section, but in particular viral infections. Examples of such viruses include, but are not limited to, lentivirus infections such as, equine infectious anaemia virus, caprine arthritis virus, visna virus, or maedi virus or retrovirus infections, such as but not limited to feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus or other retroviral infections.

5 The invention will now be described by reference to the following biological examples which are merely illustrative and are not to be construed as a limitation of
10 the scope of the present invention.

BIOLOGICAL EXAMPLES

The cytokine-inhibiting effects of compounds of the present invention may be determined by the following *in vitro* assays:

15 Assays for Interleukin - 1 (IL-1), Interleukin -8 (IL-8), and Tumour Necrosis Factor (TNF) are well known in the art, and may be found in a number of publications, and patents. Representative suitable assays for use herein are described in Adams et al., US 5,593,992, whose disclosure is incorporated by reference in its entirety.

20 **In vivo TNF assay:**

(1) Griswold *et al.*, *Drugs Under Exp. and Clinical Res.*, XIX (6), 243-248 (1993); or
(2) Boehm, *et al.*, *Journal Of Medicinal Chemistry* 39, 3929-3937 (1996)
whose disclosures are incorporated by reference herein in their entirety.

25

LPS-induced TNF α Production in Mice and Rats

In order to evaluate in vivo inhibition of LPS-induced TNF α production in rodents, both mice and rats are injected with LPS.

Mouse Method

30 Male Balb/c mice from Charles River Laboratories are pretreated (30 minutes) with compound or vehicle. After the 30 min. pretreat time, the mice are given LPS (lipopolysaccharide from *Escherichia coli* Serotype 055-85, Sigma Chemical Co., St Louis, MO) 25 ug/mouse in 25 ul phosphate buffered saline (pH 7.0) intraperitoneally. Two hours later the mice are killed by CO₂ inhalation and
35 blood samples are collected by exsanguination into heparinized blood collection tubes and stored on ice. The blood samples are centrifuged and the plasma collected and stored at -20°C until assayed for TNF α by ELISA.

Rat Method

Male Lewis rats from Charles River Laboratories are pretreated at various times with compound or vehicle. After a determined pretreat time, the rats are given 5 LPS (lipopolysaccharide from *Escherichia coli* Serotype 055-85, Sigma Chemical Co., St Louis, MO) 3.0 mg/kg intraperitoneally. The rats are killed by CO₂ inhalation and heparinized whole blood is collected from each rat by cardiac puncture 90 minutes after the LPS injection. The blood samples are centrifuged and the plasma collected for analysis by ELISA for TNF α levels.

10

ELISA Method

TNF α levels were measured using a sandwich ELISA, as described in Olivera et al., Circ. Shock, 37, 301-306, (1992), whose disclosure is incorporated by reference in its entirety herein, using a hamster monoclonal antimurine TNF α (Genzyme, 15 Boston, MA) as the capture antibody and a polyclonal rabbit antimurine TNF α (Genzyme) as the second antibody. For detection, a peroxidase-conjugated goat antirabbit antibody (Pierce, Rockford, IL) was added, followed by a substrate for peroxidase (1 mg/ml orthophenylenediamine with 1% urea peroxide). TNF α levels in the plasma samples from each animal were calculated from a standard curve generated 20 with recombinant murine TNF α (Genzyme).

LPS-Stimulated Cytokine Production in Human Whole Blood

Assay: Test compound concentrations were prepared at 10 X concentrations and LPS prepared at 1 μ g/ml (final conc. of 50 ng/ml LPS) and added in 50 μ L volumes 25 to 1.5 mL eppendorf tubes. Heparinized human whole blood was obtained from healthy volunteers and was dispensed into eppendorf tubes containing compounds and LPS in 0.4 mL volumes and the tubes incubated at 37 C. Following a 4 hour incubation, the tubes were centrifuged at 5000 rpm for 5 minutes in a Tomy microfuge, plasma was withdrawn and frozen at -80 C.

30

Cytokine measurement: IL-1 and/or TNF were quantified using a standardized ELISA technology. An in-house ELISA kit was used to detect human IL-1 and TNF. Concentrations of IL-1 or TNF were determined from standard curves of the appropriate cytokine and IC₅₀ values for test compound (concentration that inhibited 35 50% of LPS-stimulated cytokine production) were calculated by linear regression analysis.

Cytokine Specific Binding Protein Assay

A radiocompetitive binding assay was developed to provide a highly reproducible primary screen for structure-activity studies. This assay provides many advantages over the conventional bioassays which utilize freshly isolated human monocytes as a source of cytokines and ELISA assays to quantify them. Besides being a much more facile assay, the binding assay has been extensively validated to highly correlate with the results of the bioassay. A specific and reproducible cytokine inhibitor binding assay was developed using soluble cytosolic fraction from THP.1 cells and a radiolabeled compound. Patent Application USSN 08/123175 Lee et al., filed September 1993, USSN; Lee et al., PCT 94/10529 filed 16 September 1994 and Lee et al., *Nature* 300, n(72), 739-746 (Dec. 1994) whose disclosures are incorporated by reference herein in its entirety describes the above noted method for screening drugs to identify compounds which interact with and bind to the cytokine specific binding protein (hereinafter CSBP). However, for purposes herein the binding protein may be in isolated form in solution, or in immobilized form, or may be genetically engineered to be expressed on the surface of recombinant host cells such as in phage display system or as fusion proteins. Alternatively, whole cells or cytosolic fractions comprising the CSBP may be employed in the screening protocol. Regardless of the form of the binding protein, a plurality of compounds are contacted with the binding protein under conditions sufficient to form a compound/ binding protein complex and compound capable of forming, enhancing or interfering with said complexes are detected.

CSBP Kinase Assay:

This assay measures the CSBP-catalyzed transfer of ^{32}P from [α - ^{32}P]ATP to threonine residue in an epidermal growth factor receptor (EGFR)-derived peptide (T669) with the following sequence: KRELVEPLTPSGEAPNQALLR (residues 661-681). (See Gallagher et al., "Regulation of Stress Induced Cytokine Production by Pyridinyl Imidazoles: Inhibition of CSPB Kinase", *BioOrganic & Medicinal Chemistry*, 1997, 5, 49-64).

Kinase reactions (total volume 30 μl) contain: 25 mM Hepes buffer, pH 7.5; 10 mM MgCl_2 ; 170 μM ATP⁽¹⁾; 10 μM Na ortho vanadate; 0.4 mM T669 peptide; and 20-80 ng of yeast-expressed purified CSBP2 (see Lee et al., *Nature* 300, n(72), 739-746 (Dec. 1994)). Compounds (5 μl from [6X] stock⁽²⁾) are pre-incubated with the enzyme and peptide for 20 min on ice prior to starting the reactions with $^{32}\text{P}/\text{MgATP}$. Reactions are incubated at 30 °C for 10 min and stopped by adding 10

ul of 0.3 M phosphoric acid. 32P-labeled peptide is separated on phosphocellulose (Wattman, p81) filters by spotting 30 ul reaction mixture. Filters are washed 3 times with 75 mM phosphoric acid followed by 2 washes with H₂O, and counted for 32P.

5 (1) The Km of CSBP for ATP was determined to be 170 uM. Therefore, compounds screened at the Km value of ATP.

(2) Compounds are usually dissolved in DMSO and are diluted in 25 mM Hepes buffer to get final concentration of DMSO of 0.17%.

Representative compounds of Formula (I), Examples 2 to 18 have all demonstrated positive inhibitory activity of an IC₅₀ of < 50uM in this binding assay.

10

A minor variation of the above assay is shown below:

Reactions were carried in round bottom 96 well plate (from Corning) in a 30 ml volume. Reactions contained (in final concentration): 25 mM Hepes, pH7.5; 8 mM MgCl₂; 0.17 mM ATP (the Km[ATP] of p38 (see Lee et al., Nature 300, n72 pg 15 639-746 (Dec. 1994)); 2.5 uCi of [g-32P]ATP; 0.2 mM sodium orthovanadate; 1 mM DTT; 0.1% BSA; 10% glycerol; 0.67 mM T669 peptide; and 2-4 nM of yeast-expressed, activated and purified p38. Reactions were initiated by the addition of [gamma-32P]Mg/ATP, and incubated for 25 min at 37 °C. Inhibitors (dissolved in DMSO) were incubated with the reaction mixture on ice for 30 minutes prior to 20 adding the 32P-ATP. Final DMSO concentration was 0.16%. Reactions were terminated by adding 10 ul of 0.3 M phosphoric acid, and phosphorylated peptide was isolated from the reactions by capturing it on p81 phosphocellulose filters. Filters were washed with 75 mM phosphoric acids, and incorporated 32P was quantified using beta scintillation counter. Under these conditions, the specific 25 activity of p38 was 400-450 pmol/pmol enzyme, and the activity was linear for up to 2 hr of incubation. The kinase activity values were obtained after subtracting values generated in the absence of substrate which were 10-15% of total values.

Representative final compounds of Formula (I), Example 20 (Example 99), 21 (example 100), 23 (Example 98) and 27 (Example 97) have demonstrated positive 30 inhibitory activity of an IC₅₀ of < 50uM in this kinase assay.

Synthetic Examples 95, 96, 101, 102, 104 to 119, 122 to 129 have demonstrated positive inhibitory activity of an IC₅₀ of < 50uM in this kinase assay.

The compounds in the array of Table 1 were tested at screening concentration levels of 3uM or 17uM and not all compounds in this Table were found to be active 35 at this concentration.

Prostaglandin endoperoxide synthase-2 (PGHS-2) assay:

This assay describes a method for determining the inhibitory effects of compounds of Formula (I) on human PGHS-2 protein expression in LPS stimulated human monocytes. A suitable assay for PGHS-2 protein expression may be found in a number of publications, including US Patent 5,593,992 whose disclosure is incorporated herein by reference.

TNF- α in Traumatic Brain Injury Assay

This assay provides for examination of the expression of tumor necrosis factor mRNA in specific brain regions which follow experimentally induced lateral fluid-percussion traumatic brain injury (TBI) in rats. Since TNF- α is able to induce nerve growth factor (NGF) and stimulate the release of other cytokines from activated astrocytes, this post-traumatic alteration in gene expression of TNF- α plays an important role in both the acute and regenerative response to CNS trauma. A suitable assay may be found in WO 97/35856 whose disclosure is incorporated herein by reference.

CNS Injury model for IL- β mRNA

This assay characterizes the regional expression of interleukin-1 β (IL-1 β) mRNA in specific brain regions following experimental lateral fluid-percussion traumatic brain injury (TBI) in rats. Results from these assays indicate that following TBI, the temporal expression of IL-1 β mRNA is regionally stimulated in specific brain regions. These regional changes in cytokines, such as IL-1 β play a role in the post-traumatic pathologic or regenerative sequelae of brain injury. A suitable assay may be found in WO 97/35856 whose disclosure is incorporated herein by reference.

Angiogenesis Assay:

Described in WO 97/32583, whose disclosure is incorporated herein by reference, is an assay for determination of inflammatory angiogenesis which may be used to show that cytokine inhibition will stop the tissue destruction of excessive or inappropriate proliferation of blood vessels.

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, all 5 solvents are highest available purity and all reactions run under anhydrous conditions in an argon atmosphere unless otherwise indicated.

In the Examples, all temperatures are in degrees Centigrade (°C). Mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment or on a micromass platform electrospray ionization mass spectrometer 10 in the positive ion mode using 95:5 CH₃CN/CH₃OH with 1% formic acid as the carrier solvent, unless otherwise indicated. ¹H-NMR (hereinafter "NMR") spectra were recorded at 250 MHz using a Bruker AM 250 or Am 400 spectrometer. Multiplicities indicated are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br indicates a broad signal. Sat. indicates a saturated solution, eq indicates the 15 proportion of a molar equivalent of reagent relative to the principal reactant.

Flash chromatography is run over Merck Silica gel 60 (230 - 400 mesh).

Example 1

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl)imidazole

20 a) 2-Methylthiopyrimidine-4-carboxaldehyde dimethyl acetal
Pyruvic aldehyde dimethyl acetal (60 milliliter (hereinafter "mL"), 459 millimole (hereinafter "mmol")) and N,N-dimethyl formamide dimethyl acetal (60 mL, 459 mmol) were stirred together at 100°C for 18 hours (hereinafter "h"). The mixture was cooled.

25 Methanol (300 mL), thiourea (69.6 g) and sodium methoxide (231 mL, 25 wt% in MeOH) were added to the above mixture and stirred at 70°C for 2 h. After cooling, iodomethane (144 mL) was added dropwise and the mixture was stirred 3 h. at room temp. After diluting with EtOAc and H₂O, the organic phase was separated, dried (Na₂SO₄), and concentrated to yield the title compound as a brown oil (75.5

30 gram (hereinafter 'g'), 82% yield). ¹H NMR (CDCl₃): d 8.17 (d, 1H), 6.77 (d, 1H), 5.15 (s, 1H), 3.40 (s, 6H).

35 b) 2-Methylthiopyrimidine-4-carboxaldehyde
The product of example 1(a) (9.96 g, 50 mmol), and 3 N HCl (42 mL, 126 mmol) were combined and stirred at 48°C for 16h, cooled to 23°C, combined with EtOAc (200mL) and made basic by the addition of solid Na₂CO₃ (12.6 g, 150 mmol). The aqueous phase was extracted with EtOAc (4 x 150 mL, dried

(Na₂SO₄), concentrated and the residue was filtered through a pad of silica (ca 150 mL) with CH₂Cl₂ to afford 7.49 g (97%) of the title compound ¹H NMR (CDCl₃): δ 9.96 (s, 1), 8.77 (d, 1), 7.44 (d, 1), 2.62 (s, 3).

c) 1-t-Butoxycarbonyl-4-aminopiperidine

5 1-t-Butoxycarbonyl piperidine-4-one (commercially available from Lancaster Chem) (39.9 g, 0.20 mol), THF (150 mL), H₂O (300 mL), and H₂NOH•HCl (55.2, 0.80 mol) were dissolved together and Na₂CO₃ (55.2 g, 0.53 mol) was added in small portions. The mixture was stirred at 23°C for 14 h, most of the THF was evaporated in vacuo, adjusted to pH > 10 with 50% aq NaOH, 10 extracted with EtOAc(5 x 50 mL) and concentrated to a white foam. Triturated with hexane, filtered and the solid was dried in vacuo to afford 40.31 g.

The above residue was dissolved in EtOH (abs) (1 L) and Raney Ni (50 mL of a slurry in EtOH) was added and the mixture was reduced under H₂ (50 psi) for 3.5 h. The catalyst was filtered off and washed with EtOH to afford. Concentration 15 afforde 38.44g (96% overall) of the title compound as a colorless oil which solidified to a white solid upon standing at -20°C.

d) 2-Methylthiopyrimidine-4-carboxaldehyde [1-t-butoxycarbonyl-4-aminopiperidine] imine

The product of the previous step (6.51 g, 32.6 mmol) MgSO₄ (ca 2 g), the 20 product of example 1(b) (4.84 g, 31.4 mmol), and CH₂Cl₂ (100 mL) were combined and stirred at 23°C for 16 h. Filtration and concentration of the filtrate afforded the title compound as a yellow oil. ¹H NMR (CDCl₃): δ 8.57 (d, 1), 8.27 (s, 1), 7.58 (d, 1), 4.05 (m, 2), 3.55 (m, 1), 3.00 (m, 2), 2.60 (s, 3), 1.75 (m, 4), 1.48 (s, 9).

e) 4-Fluorophenyl-tolylsulfonomethylformamide

25 To a suspension of p-toluenesulfinic acid sodium salt (30 g) in H₂O (100 mL) was added methyl t-butyl ether (50 mL) followed by dropwise addition of conc HCl (15 mL). After stirring 5 min, the organic phase was removed and the aqueous phase was extracted with methyl t-butyl ether. The organic phase was dried (Na₂SO₄) and concentrated to near dryness. Hexane was added and the resulting 30 precipitate collected to afford p-toluenesulfinic acid; yield 22 g.

p-Toluenesulfinic acid (22 g, 140.6 mmol), p-fluorobenzaldehyde (22 mL, 206 mmol), formamide (20 mL, 503 mmol) and camphor sulphonic acid (4 g, 17.3 mmol) were combined and stirred at 60 °C 18 h. The resulting solid was broken up and stirred with a mixture of MeOH (35 mL) and hexane (82 mL) then filtered. The 35 solid was resuspended in MeOH / hexanes (1:3, 200 mL) and stirred vigorously to break up the remaining chunks. Filtration afforded the title compound (27 g, 62 %

yield): ^1H NMR (400 MHz, CDCl_3) δ 8.13 (s, 1H), 7.71 (d, 2H), 7.43 (dd, 2H), 7.32 (d, 2H), 7.08 (t, 2H), 6.34 (d, 1H), 2.45 (s, 3H).

f) 4-Fluorophenyl-tolylsulfonomethylisocyanide

4-Fluorophenyl-tolylsulfonomethylformamide (2.01g, 6.25 mmol) in DME (32 mL) was cooled to -10 $^{\circ}\text{C}$. POCl_3 (1.52 mL, 16.3 mmol) was added followed by the dropwise addition of triethylamine (4.6 mL, 32.6 mmol) in DME (3mL) keeping the internal temperature below -5 $^{\circ}\text{C}$. The mixture was gradually warmed to ambient temperature over 1 h, poured into H_2O and extracted with EtOAc . The organic phase was washed with sat aq NaHCO_3 , dried (Na_2SO_4), and concentrated. The resulting residue was triturated with petroleum ether and filtered to afford the title compound (1.7 g, 90% yield): ^1H NMR (CDCl_3) δ 7.63 (d, 2H), 7.33 (m, 4H), 7.10 (t, 2H), 5.60 (s, 1H), 2.50 (s, 3H).

g) 1-[(1-t-Butoxycarbonyl)piperidin-4-yl]-4-(4-fluorophenyl)-5-[(2-methylthio(pyrimidin-4-yl)]imidazole

The product of example 1(d) and the product of the previous example (9.41 g, 32.6 mmol), DMF (64 mL) and K_2CO_3 (4.43 g, 32.4 mmol) were combined and stirred for 2 days, diluted with Et_2O and filtered. The solid was washed with Et_2O and the filtrate was concentrated to a yellow solid. Trituration of the solid with Et_2O , filtration and washing with more Et_2O and drying *in vacuo* afforded 9.07g of the title compound as a white solid (62% from the product of example 1(b)). MS ES+ m/z = 470 (MH^+).

h) 1-[(1-t-Butoxycarbonyl)piperidin-4-yl]-4-(4-fluorophenyl)-5-[(2-methylsulfonyl(pyrimidin-4-yl)]imidazole

The product of the previous example (9.07 g, 19.3 mmol), dissolved in THF was cooled to -10 $^{\circ}\text{C}$ and OXONE (28.5g, 46.4 mmol) in H_2O (250 mL) was added dropwise. The resulting mixture was stirred at 23 $^{\circ}\text{C}$ for 24h, combined with ice (100 mL) and CH_2Cl_2 (700 mL) shaken and the aqueous was separated. The organic phase was washed with brine (100 mL), dried (Na_2SO_4), concentrated and dried *in vacuo* to afford 8.27 g (85%) of the title compound as a white foam. MS ES+ m/z = 502 (MH^+).

i) 1-[(1-t-Butoxycarbonyl)piperidin-4-yl]-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

NaH (60% in mineral oil) (1.6 g, 40 mmol) was washed with dry THF and layered with more THF (75 mL) and phenol (4.14 g, 44 mmol) was added as a solid. The vigorous reaction subsided within 5 min and then the product of the previous example (5.01g, 10 mmol) was added portionwise, and the reaction was stirred 90

min, concentrated in vacuo and the residue was dissolved in CH_2Cl_2 (300 mL) and washed with 10% aq NaOH (2x) and dried (Na_2SO_4), and filtered through a pad of silica gel with 0 - 2% MeOH in CH_2Cl_2 , the desired fraction was concentrated and the residue was crystallized from acetone/hexane to afford 2.79 g (54%). MS ES+ 5 m/z = 502 (MH^+).

j) 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

The product of the previous example (3.91 g, 7.59 mmol) was combined with ice cold TFA (75 mL) and then warmed to 23° C and stirred for 15 min, and the reaction was concentrated in vacuo and the residue was dissolved in EtOAc (200 10 mL) and washed with 10% aq NaOH (2x 100 mL), dried (Na_2SO_4) concentrated and the residue was crystallized from acetone/hexane to afford 2.24 g (71%) the title compound as white crystals. mp = 182 - 183° C.

By analogous methods to that shown above, the following compounds have 15 been prepared:

Example 2

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[(2-acetamidophenoxy)pyrimidin-4-yl]imidazole

ES (+) MS m/e = 473 (MH^+)

20

Example 3

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[(3-propionamido-phenoxy)pyrimidin-4-yl]imidazole

ES (+) MS m/e = 487 (MH^+)

25

Example 4

1-Cyclohexyl-4-(4-fluorophenyl)-5-[(2-phenoxy)pyrimidin-4-yl]imidazole

ES (+) MS m/e = 415 (MH^+)

30

Example 5

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(2,6-di-methylphenoxy)pyrimidin-4-yl]imidazole

ES (+) MS m/e = 443 (MH^+)

35

Example 6:

(R)-(1-Hydroxy-3-phenylprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

ES (+) MS m/e = 467 (MH⁺)

5

Example 15

(S)-(1-Hydroxy-3-phenylprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

ES (+) MS m/e = 467 (MH⁺)

10

Example 16

(+/-)-1-(1-Phenoxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

ES (+) MS m/e = 467 (MH⁺)

15

Example 17

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(3-piperazin-1-ylamido-phenoxy)pyrimidin-4-yl]imidazole

ES (+) MS m/e = 528 (MH⁺).

20

Example 18

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(3-piperazin-1-ylacetamido)-phenoxy)pyrimidin-4-yl]imidazole

a) (4-N-t-Butoxycarbonylpiperazin-1-yl)-3-hydroxyphenylacetamide

3-Hydroxyphenylacetic acid (0.50 g, 3.3 mmol), BOC piperazine (0.737 g, 25 3.96 mmol), Et₃N (0.92 mL, 6.6 mmol), and CH₂Cl₂ (7 mL) were combined, cooled to 4° and solid Bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (0.840 g, 3.3 mmol) was added under Ar. The ice bath was removed and a clear solution was obtained on warming to 23°. After 1 hour tlc (silica plates, 19 :1 CH₂Cl₂/CH₃OH) indicated a completed reaction. The reaction was diluted with CH₂Cl₂(100 mL), 30 washed with 0.3 N HCl (20 mL), H₂O (20 mL), satd aq NaHCO₃ (20 mL) and Satd aq NaCl (20 mL), dried (Na₂SO₄) filtered and the filtrate was diluted with CH₃OH til ca 4% CH₃OH in CH₂Cl₂ and filtered through a pad of silica to afford the title compound as a white foam. ¹H NMR (CDCl₃): d 7.13 (m, 1), 6.81 (s, 1), 6.73 (d, 1), 6.68 (d, 1), 3.69 (s, 2), 3.59 (m, 2), 3.39 (m, 4), 3.22 (m, 2), 1.46 (s, 9).

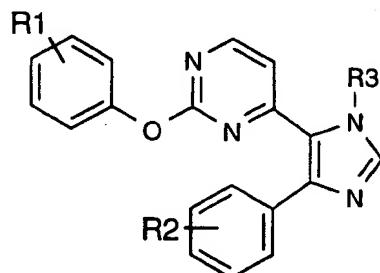
35 b) 1-(4-N-t-Butoxycarbonylpiperidinyl)-4-(4-Fluorophenyl)-5-[2-[3-[1-(4-N-t-butoxycarbonylpiperazinyl)acetamido]phenoxy]-4-pyrimidinyl]imidazole

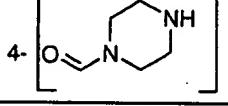
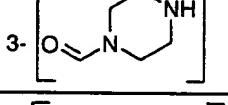
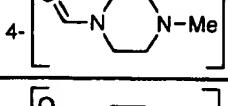
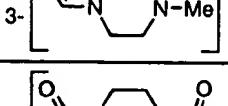
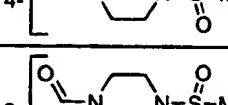
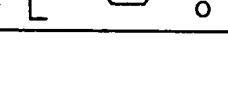
The product of the above example was reacted by the procedure of example 1(e) to afford the title compound as a white foam. ES (+) MS m/e = 742 (MH⁺).

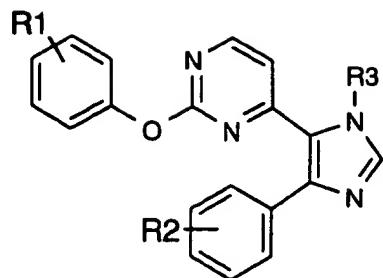
c) 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(3-piperazin-1-ylacetamido)phenoxy]pyrimidin-4-yl]imidazole

5 The product of the above example was reacted by the procedure of example 1(f) to afford the title compound as a white foam. ES (+) MS m/e = 542 (MH⁺).

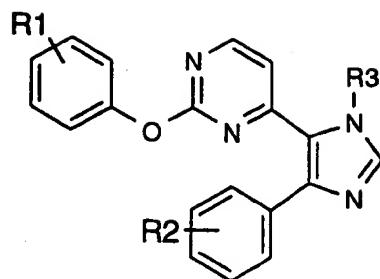
By analogous methods to those indicated above, and also as described in WO97/25045, Adams et al., whose disclosure is incorporated herein by reference in 10 its entirety, the following compounds may be prepared:



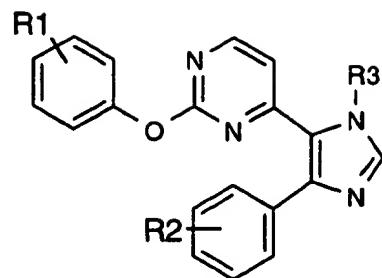
Example	R1	R2	R3
19	4-CONHMe	4-F	piperidin-4-yl
20	3-CONH ₂	4-F	piperidin-4-yl
21	3-CONHMe	4-F	piperidin-4-yl
22	4-CON(Me) ₂	4-F	piperidin-4-yl
23	3-CON(Me) ₂	4-F	piperidin-4-yl
24	4-CON(CH ₂) ₄	4-F	piperidin-4-yl
25	3-CON(CH ₂) ₄	4-F	piperidin-4-yl
26	4-CON(CH ₂) ₅	4-F	piperidin-4-yl
27	3-CON(CH ₂) ₅	4-F	piperidin-4-yl
28	4- 	4-F	piperidin-4-yl
29	3- 	4-Cl	piperidin-4-yl
30	4- 	4-F	piperidin-4-yl
31	3- 	4-F	piperidin-4-yl
32	4- 	4-F	piperidin-4-yl
33	3- 	4-F	piperidin-4-yl



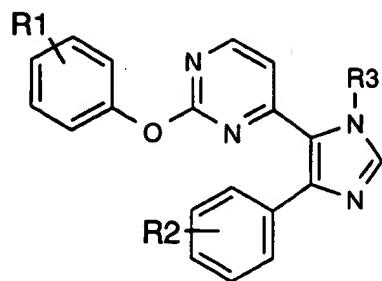
Example	R1	R2	R3
34	4-SO ₂ NHMe	4-F	piperidin-4-yl
35	3- SO ₂ NH ₂	4-F	piperidin-4-yl
36	3- SO ₂ NHMe	4-F	piperidin-4-yl
37	4- SO ₂ N(Me) ₂	4-F	piperidin-4-yl
38	3- SO ₂ N(Me) ₂	4-F	piperidin-4-yl
39	4- SO ₂ N(CH ₂) ₄	4-F	piperidin-4-yl
40	3- SO ₂ N(CH ₂) ₄	4-F	piperidin-4-yl
41	4- SO ₂ N(CH ₂) ₅	4-F	piperidin-4-yl
42	3- SO ₂ N(CH ₂) ₅	4-F	piperidin-4-yl
43	4-	4-F	piperidin-4-yl
44	3-	4-F	piperidin-4-yl
45	4-	4-F	piperidin-4-yl
46	3-	4-F	piperidin-4-yl
47	4-	4-H	piperidin-4-yl
48	3-	3-Cl	piperidin-4-yl



Example	R1	R2	R3
49	4-NHSO ₂ Me	4-F	piperidin-4-yl
50	3-NHSO ₂ Me	4-F	piperidin-4-yl
51	3-NHSO ₂ Ph	4-F	piperidin-4-yl
52	4-NMeSO ₂ Me	4-F	piperidin-4-yl
53	3-NMeSO ₂ Me	4-F	piperidin-4-yl
54	3-NMeSO ₂ Ph	4-F	piperidin-4-yl
55	3-SO ₂ Me	4-F	piperidin-4-yl
56	3-SO ₂ Et	4-F	piperidin-4-yl
57	4-SO ₂ Et	4-F	piperidin-4-yl
58	3-SO ₂ NHCH ₂ CH ₂ N(Me) ₂	4-F	piperidin-4-yl
59	4-SO ₂ NHCH ₂ CH ₂ N(Me) ₂	4-F	piperidin-4-yl
60	4-NHSO ₂ Ph	4-F	piperidin-4-yl
61	4-NHSO ₂ Me	3-Cl	piperidin-4-yl
62	4-NHSO ₂ Me	4-H	piperidin-4-yl
63	3-SO ₂ Me	3-Cl	piperidin-4-yl



Example	R1	R2	R3
64	4-CH ₂ CONHMe	4-F	piperidin-4-yl
65	3-CH ₂ CONH ₂	4-F	piperidin-4-yl
66	3-CH ₂ CONHMe	4-F	piperidin-4-yl
67	4-CH ₂ CON(Me) ₂	4-F	piperidin-4-yl
68	3-CH ₂ CON(Me) ₂	4-F	piperidin-4-yl
69	4-CH ₂ CON(CH ₂) ₄	4-F	piperidin-4-yl
70	3-CH ₂ CON(CH ₂) ₄	4-F	piperidin-4-yl
71	4-CH ₂ CON(CH ₂) ₅	4-F	piperidin-4-yl
72	3-CH ₂ CON(CH ₂) ₅	4-F	piperidin-4-yl
73	4-[4-F	piperidin-4-yl
74	3-[3-Cl	piperidin-4-yl
75	4-[4-F	piperidin-4-yl
76	3-[4-F	piperidin-4-yl
77	4-[4-F	piperidin-4-yl
78	3-[4-F	piperidin-4-yl



Example	R1	R2	R3
79	4-CONHMe	4-Me	piperidin-4-yl
80	3-CONH ₂	4-Me	piperidin-4-yl
81	3-CONHMe	4-Me	piperidin-4-yl
82	4-CON(Me) ₂	4-Me	piperidin-4-yl
83	3-CON(Me) ₂	4-Me	piperidin-4-yl
84	4-NHSO ₂ Me	4-Me	piperidin-4-yl
85	3-NHSO ₂ Me	4-Me	piperidin-4-yl
86	3-NHSO ₂ Ph	4-Me	piperidin-4-yl
87	3-SO ₂ Me	4-Me	piperidin-4-yl
88	3-SO ₂ Et	4-Me	piperidin-4-yl
89	4-SO ₂ Et	4-Me	piperidin-4-yl
90	3-SO ₂ NHCH ₂ CH ₂ N(Me) ₂	4-Me	piperidin-4-yl
91	4-CH ₂ CONH ₂	4-Me	piperidin-4-yl
92	3-CH ₂ CONH ₂	4-Me	piperidin-4-yl
93	3-CH ₂ CONMe ₂	4-F	piperidin-4-yl

Using solution phase synthesis the following compounds have been prepared:

Example 94

5 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-phenoxyypyrimidin-4-yl)imidazole

a) 2-Propylthiopyrimidine-4-carboxaldehyde dimethyl acetal

Charge a 1 L 3-necked flask equipped with a stir bar, thermometer, 100 mL addition funnel and reflux condenser with N,N-dimethylformamide dimethyl acetal (88.7 g, 98.9 mL, 700 mmol) and pyruvaldehyde dimethyl acetal (85.3 g, 86.8 mL, 700 mmol) and heat in an oil bath at 110 °C for 3-4 h. Cool the solution to 85 °C and add thiourea (48.9 g, 636.4 mmol) and NaOMe (25 wt % in MeOH, 151.2 g, 160 mL, 700 mmol) and stir at 85 °C for 3-4 h. Cool the solution to 65 °C and charge 1-bromoropane (86.9 g, 64.4 mL, 700 mmol) to the addition funnel and add slowly over 10-15 min to the reaction, bringing the solution to a mild reflux. After 1 h, add 100 mL of EtOAC to the reaction and bring the oil bath temperature to 95 °C. Replace the reflux condenser with a distillation head and distill 150-200 mL of solvent from the reaction. Add an additional 400 mL of EtOAC and 120 mL of H₂O and stir at 50 °C for 5 min. Transfer to a separatory funnel and separate the aqueous phase. Add 60 mL of H₂O, agitate, and separate the aqueous phase.

A sample was concentrated to give a yellow oil: 1H NMR (300 MHz, CDCl₃) d 8.53 (1H, d, J 5.0 Hz), 7.16 (1H, d, J = 5.0 Hz), 5.17 (1H, s), 3.42 (3H, s), 3.14 (2H, t, J = 7.3 Hz), 1.76 (2H, m), 1.05 (3H, t, J = 7.3 Hz).

b) 2-Propylthiopyrimidine-4-carboxaldehyde

The product of example 1(a) (10.0 g, 50 mmol), and 3 N HCl (42 mL, 126 mmol) were combined and stirred at 48 °C for 16h, cooled to 23 °C, combined with EtOAc (200mL) and made basic by the addition of solid Na₂CO₃ (12.6 g, 150 mmol). The aqueous phase was extracted with EtOAc (4 x 150 mL, dried (Na₂SO₄), concentrated and the residue was filtered through a pad of silica (ca 150 mL) with CH₂Cl₂ to afford 7.49 g (97%) of the title compound 1H NMR (400 MHz, CDCl₃): d 9.95 (s, 1H), 8.78 (d, 1H), 7.45 (d, 1H), 3.21 (t, 2H), 1.82 (m, 2H), 1.1 (t, 3H).

30 c) 1-t-Butoxycarbonyl-4-aminopiperidine

1- t-Butoxycarbonyl piperidine-4-one (commercially available from Lancaster Chem) (39.9 g, 0.20 mol) , THF (150 mL), H₂O (300 mL), and H₂NOH •HCl (55.2, 0.80 mol) were dissolved together and Na₂CO₃ (55.2 g, 0.53 mol) was added in small portions. The mixture was stirred at 23 °C for 14 h, most of the THF was evaporated in vacuo, adjusted to pH > 10 with 50% aq NaOH, extracted with EtOAc(5 x 50 mL) and

concentrated to a white foam. Triturated with hexane, filtered and the solid was dried in vacuo to afford 40.31 g.

5 The above residue was dissolved in EtOH (abs) (1 L) and Raney Ni (50 mL of a slurry in EtOH) was added and the mixture was reduced under H₂ (50 psi) for 3.5 h. The catalyst was filtered off and washed with EtOH to afford. Concentration afforde 38.44g (96% overall) of the title compound as a colorless oil which solidified to a white solid upon standing at -20°C.

d) 2-Methylthiopyrimidine-4-carboxaldehyde [1-t-butoxycarbonyl-4-aminopiperidine] imine

10 The product of the previous step (6.51 g, 32.6 mmol) MgSO₄ (ca 2 g), the product of example 1(b) (4.84 g, 31.4 mmol), and CH₂Cl₂ (100 mL) were combined and stirred at 23°C for 16 h. Filtration and concentration of the filtrate afforded the title compound as a yellow oil. ¹H NMR (CDCl₃): d 8.57 (d, 1), 8.27 (s, 1), 7.58 (d, 1), 4.05 (m, 2), 3.55 (m, 1), 3.00 (m, 2), 2.60 (s, 3), 1.75 (m, 4), 1.48 (s, 9).

15 e) 4-Fluorophenyl-tolylsulfonomethylformamide

To a suspension of p-toluenesulfinic acid sodium salt (30 g) in H₂O (100 mL) was added methyl t-butyl ether (50 mL) followed by dropwise addition of conc HCl (15 mL). After stirring 5 min, the organic phase was removed and the aqueous phase was extracted with methyl t-butyl ether. The organic phase was dried (Na₂SO₄) and concentrated to near dryness. Hexane was added and the resulting precipitate collected to afford p-toluenesulfinic acid; yield 22 g.

20 p-Toluenesulfinic acid (22 g, 140.6 mmol), p-fluorobenzaldehyde (22 mL, 206 mmol), formamide (20 mL, 503 mmol) and camphor sulphonic acid (4 g, 17.3 mmol) were combined and stirred at 60 °C 18 h. The resulting solid was broken up and stirred with a mixture of MeOH (35 mL) and hexane (82 mL) then filtered. The solid was resuspended in MeOH / hexanes (1:3, 200 mL) and stirred vigorously to break up the remaining chunks. Filtration afforded the title compound (27 g, 62 % yield): ¹H NMR (400 MHz, CDCl₃) d 8.13 (s, 1H), 7.71 (d, 2H), 7.43 (dd, 2H), 7.32 (d, 2H), 7.08 (t, 2H), 6.34 (d, 1H), 2.45 (s, 3H).

25 f) 4-Fluorophenyl-tolylsulfonomethylisocyanide

30 4-Fluorophenyl-tolylsulfonomethylformamide (2.01g, 6.25 mmol) in DME (32 mL) was cooled to -10 °C. POCl₃ (1.52 mL, 16.3 mmol) was added followed by the dropwise addition of triethylamine (4.6 mL, 32.6 mmol) in DME (3mL) keeping the internal temperature below -5 °C. The mixture was gradually warmed to ambient temperature over 1 h, poured into H₂O and extracted with EtOAc. The organic phase was washed with sat aq NaHCO₃, dried (Na₂SO₄), and concentrated. The resulting residue was triturated with

petroleum ether and filtered to afford the title compound (1.7 g, 90% yield): ^1H NMR (CDCl_3) δ 7.63 (d, 2H), 7.33 (m, 4H), 7.10 (t, 2H), 5.60 (s, 1H), 2.50 (s, 3H).

g) 1-[1-t-Butoxycarbonyl)piperidin-4-yl]-4-(4-fluorophenyl)-5-[(2-methylthio)-(pyrimidin-4-yl)]imidazole

5 The product of example 1(d) and the product of the previous example (9.41 g, 32.6 mmol), DMF (64 mL) and K_2CO_3 (4.43 g, 32.4 mmol) were combined and stirred for 2 days, diluted with Et_2O and filtered. The solid was washed with Et_2O and the filtrate was concentrated to a yellow solid. Trituration of the solid with Et_2O , filtration and washing with more Et_2O and drying *in vacuo* afforded 9.07 g of the title compound as a white solid

10 (62% from the product of example 1(b)). MS ES+ m/z = 470 (MH^+).

h) 1-[1-t-Butoxycarbonyl)piperidin-4-yl]-4-(4-fluorophenyl)-5-[(2-methylsulfonyl)(pyrimidin-4-yl)]imidazole

The product of the previous example (9.07 g, 19.3 mmol), dissolved in THF was cooled to -10°C and OXONE (28.5 g, 46.4 mmol) in H_2O (250 mL) was added dropwise.

15 The resulting mixture was stirred at 23°C for 24h, combined with ice (100 mL) and CH_2Cl_2 (700 mL) shaken and the aqueous was separated. The organic phase was washed with brine (100 mL), dried (Na_2SO_4), concentrated and dried *in vacuo* to afford 8.27 g (85%) of the title compound as a white foam. MS ES+ m/z = 502 (MH^+).

i) 1-[1-t-Butoxycarbonyl)piperidin-4-yl]-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

20 NaH (60% in mineral oil) (1.6 g, 40 mmol) was washed with dry THF and layered with more THF (75 mL) and phenol (4.14 g, 44 mmol) was added as a solid. The vigorous reaction subsided within 5 min and then the product of the previous example (5.01 g, 10 mmol) was added portionwise, and the reaction was stirred 90 min, concentrated in *vacuo* and the residue was dissolved in CH_2Cl_2 (300 mL) and washed with 10% aq NaOH (2x) and dried (Na_2SO_4), and filtered through a pad of silica gel with 0 - 2% MeOH in CH_2Cl_2 , the desired fraction was concentrated and the residue was crystallized from acetone/hexane to afford 2.79 g (54%). MS ES+ m/z = 502 (MH^+).

j) 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

25 The product of the previous example (3.91 g, 7.59 mmol) was combined with ice cold TFA (75 mL) and then warmed to 23°C and stirred for 15 min, and the reaction was concentrated in *vacuo* and the residue was dissolved in EtOAc (200 mL) and washed with 10% aq NaOH (2x 100 mL), dried (Na_2SO_4) concentrated and the residue was crystallized from acetone/hexane to afford 2.24 g (71%) the title compound as white crystals. mp =

30 182 - 183 $^\circ\text{C}$.

Example 951-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(3-piperazin-1-ylamido)-phenoxy]pyrimidin-4-yl]imidazolea) (4-N-t-Butoxycarbonylpiperazin-1-yl)-3-hydroxybenzamide

5 3-Hydroxybenzoic acid (0.483 g, 3.5 mmol), BOC piperazine (0.737 g, 3.96 mmol), Et₃N (0.92 mL, 6.6 mmol), and CH₂Cl₂ (10 mL) were combined, cooled to 4° and solid Bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (0.889 g, 3.5 mmol) was added under Ar. The ice bath was removed and a clear solution was obtained on warming to 23°. After 1 h tlc (silica plates, 19 :1 CH₂Cl₂/CH₃OH) indicated a completed reaction. The reaction was 10 diluted with CH₂Cl₂ (100 mL), washed with 0.3 N HCl (20 mL), H₂O (20 mL), satd aq NaHCO₃ (20 mL) and satd aq NaCl (20 mL), dried (Na₂SO₄) filtered and concentrated to afford the title compound as a white foam. ¹H NMR (CDCl₃): d 7.20 (m, 1), 6.90 (s, 1), 6.86 (d, 1), 6.82 (d, 1), 3.69 (m, 2), 3.59 (m, 2), 3.39 (m, 4), 1.46 (s, 9).

b) 1-(4-N-t-Butoxycarbonylpiperidinyl)-4-(4-Fluorophenyl)-5-[2-[3-[1-(4-N-t-butoxycarbonylpiperazinyl)amido]phenoxy]-4-pyrimidinyl]imidazole

15 The product of the above example was reacted by the procedure of example 1(i) to afford the title compound as a white foam. ES (+) MS m/e = 728 (MH⁺).

c) 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(3-piperazin-1-ylamido)-phenoxy]pyrimidin-4-yl]imidazole

20 The product of the above example was reacted by the procedure of example 1(j) to afford the title compound as a white foam. ES (+) MS m/e = 528 (MH⁺).

Example 961-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-isopropylcarboxamido-phenoxy]pyrimidin-4-yl]imidazolea) (N-Isopropyl)-3-hydroxybenzamide

25 3-Hydroxybenzoic acid (0.966 g, 7.0 mmol), N-methylmorpholine (2.3 mL, 21 mmol), iso-propylamine (1.78 mL, 21 mmol) and CH₂Cl₂ (30 mL) were dissolved together and hydroxybenzotriazole (1.03 g, 7.7 mmol) and 1-[3-(dimethylamino)propyl]-3-30 ethylcarbodiimide hydrochloride (1.47 g, 7.7 mmol) was added; stirred 16 h, diluted with CH₂Cl₂ (70 mL) and the organic phase was washed with satd aq NaHCO₃, H₂O, 0.3 N HCl, H₂O, and satd aq NaCl, dried (Na₂SO₄) and concentrated to afford 443 mg as a white foam. ¹H NMR (CDCl₃): d 7.23 (m, 3), 6.90 (m, 1), 4.22 (m, 1), 1.25 (d, 6).

b) 1-(4-N-t-Butoxycarbonylpiperidinyl)-4-(4-Fluorophenyl)-5-[2-(3-N-isopropyl-carboxamido]phenoxy]pyrimidin-4-yl]imidazole

The product of the above example was reacted by the procedure of example 1(i) to afford the title compound as a white foam. ES (+) MS m/e = 601 (MH⁺).

c) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-isopropyl-carboxamido-phenoxy)pyrimidin-4-yl]imidazole

5 The product of the above example was reacted by the procedure of example 1(j) to afford the title compound as a white foam. ES (+) MS m/e = 528 (MH⁺).

Example 97

10 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-piperidinylcarboxamido-phenoxy)pyrimidin-4-yl]imidazole

a) (N-Piperidinyl)-3-hydroxybenzamide
By the procedure of 95(a) (BOP-Cl coupling) except using piperidine as the nucleophilic amine afforded the title compound as a white foam. ¹H NMR (CDCl₃): δ 7.22 (m, 1), 6.87 (m, 1), 6.80 (m, 2), 3.67 (m, 2), 3.37 (m, 2), 1.67 (m, 4), 1.52 (m, 2).

15 b) 1-(4-N-t-Butoxycarbonylpiperidinyl)-4-(4-fluorophenyl)-5-[2-(3-N-piperidinylcarboxamidophenoxy)pyrimidin-4-yl]imidazole
The product of the above example was reacted by the procedure of example 1(i) (phenoxide displacement on the pyrimidine sulfone) to afford the title compound as a white foam. ES (+) MS m/e = 637 (MH⁺).

20 c) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-piperidinylcarboxamidophenoxy)pyrimidin-4-yl]imidazole
The product of the above example was reacted by the procedure of example 1(j) (TFA cleavage of BOC and OH⁻ neutralization) to afford the title compound as a white foam. ES (+) MS m/e = 527 (MH⁺).

25

Example 98

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-dimethylcarboxamido-phenoxy)pyrimidin-4-yl]imidazole

a) (N-Dimethyl)-3-hydroxybenzamide
30 By the procedure of 95(a) except using dimethylamine as the nucleophilic amine afforded the title compound as a white foam. ¹H NMR (CDCl₃): δ 7.23 (m, 1), 6.85 (m, 3), 3.67 (m, 2), 1.88 (s, 3), 1.76 (s, 3).

b) 1-(4-N-t-Butoxycarbonylpiperidinyl)-4-(4-Fluorophenyl)-5-[2-(3-N-dimethylcarboxamidophenoxy)pyrimidin-4-yl]imidazole
35 The product of the above example was reacted by the procedure of example 1(i) to afford the title compound as a white foam. ES (+) MS m/e = 587 (MH⁺).

c) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-dimethylcarboxamidophenoxy)pyrimidin-4-yl]imidazole

The product of the above example was reacted by the procedure of example 1(j) to afford the title compound as a white foam. ES (+) MS m/e = 487 (MH⁺).

5

Example 99

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-carboxamidophenoxy)pyrimidin-4-yl]imidazole

a) 3-Hydroxybenzamide- O-TBDMS ether

10 3-Hydroxy-methylbenzoate O-TBDMS ether (Cushman,M.; Nagarathnam,D.; Geahlen, R. L. *J. Nat. Prod.* 1991, 54, 1345-1352.) (2.66 g, 10 mmol) in toluene (20 mL) was treated dropwise with the Aluminum amide prepared from NH4Cl (100 mmol) by the method of Weinreb (Levin,J.L.; Turos,E.; Weinreb,S.M. *Synth Commun.*, 1982, 12, 989-993) as a solution in toluene (120 mL) and the resulting mixture was heated to 90° for 1h, 15 cooled to 4° and 5% aq HCl (100 mL) was added. Phases were separated and the aq was extracted with EtOAc. The combined organic phases were dried (Na2SO4) and concentrated to afford 2.03g . ES (+) MS m/e = 252 (MH⁺).

b) 3-Hydroxybenzamide

20 The product of the preceedeng example (1.73g, 6.89 mmol) was combined with 1M TBAF in THF (10 mL, 10 mmol) and stirred 10 min. The reaction was washed with CH2Cl2 and no product could be extracted. The aq phase was concentrated and the dry residue was dissolved in CH2Cl2 and filtered through a plug of silica with 0-5% CH3OH in CH2Cl2. The chromatographed material was concentrated and the residue was triturated with CH2Cl2, filtered and washed with CH2Cl2 (3X) to afford a white solid (270 mg). 25 ¹H NMR (CDCl₃): d 7.27 (m, 3), 7.00 (m, 1).

c) 1-(4-N-t-Butoxycarbonylpiperidinyl)-4-(4-fluorophenyl)-5-[2-(3-N-carboxamidophenoxy)pyrimidin-4-yl]imidazole

The product of the above example was reacted by the procedure of example 1(i) to afford the title compound as a white foam. ES (+) MS m/e = 559 (MH⁺).

30 d) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-carboxamidophenoxy)pyrimidin-4-yl]imidazole

The product of the above example was reacted by the procedure of example 1(j) to afford the title compound as a white foam. ES (+) MS m/e = 459 (MH⁺).

Example 1001-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-methylcarboxamidophenoxy)pyrimidin-4-yl]imidazolea) 3-(N-methyl)-3-hydroxybenzamide

5 By the procedure of 96(a) (EDC coupling) except using methylamine as the nucleophilic amine afforded the title compound as a white solid. ^1H NMR (CDCl_3): δ 7.16 (m, 3), 6.91 (m, 1), 2.86 (s, 3).

b) 1-(4-N-t-Butoxycarbonylpiperidinyl)-4-(4-Fluorophenyl)-5-[2-(3-N-methylcarboxamidophenoxy)pyrimidin-4-yl]imidazole

10 The product of the above example was reacted by the procedure of example 1(i) to afford the title compound as a white foam. ES (+) MS m/e = 573 (MH^+).

c) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-methylcarboxamido-phenoxy)pyrimidin-4-yl]imidazole

15 The product of the above example was reacted by the procedure of example 1(j) to afford the title compound as a white foam. ES (+) MS m/e = 473 (MH^+).

Example 101trans-1-(4-Hydroxymethylcyclohexyl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazolea) Ethyl 4-oxocyclohexanecarboxylate

20 To a solution of ethyl 4-hydroxycyclohexanecarboxylate (16 g, 93 mmol), 4-methylmorpholine N-oxide (16.32 g, 139.5 mmol) and CH_2Cl_2 (180 mL) was added tetrapropylammonium perruthenate (0.8 g, 2.3 mmol) in small portions at a rate that maintained the reaction temperature at 35-40°. The reaction slowly cooled and was stirred overnight. The resulting mixture was filtered through silica with CH_2Cl_2 to afford 13.46 g (85%) of the title compound as a colorless oil. ^1H NMR (CDCl_3): δ 4.19 (q, 2), 2.75 (m, 1), 2.5 (m, 2), 2.37 (m, 2), 2.19 (m, 2), 2.04 (m, 2).

b) Ethyl 4-dibenzylaminocyclohexanecarboxylate

30 To a solution of the product of the preceding reaction (13.46g, 79.2 mmol), dibenzylamine (17.3 mL, 87.1 mmol) and dichloroethane (270 mL) was added $\text{NaBH}(\text{OAc})_3$ (23.5 g, 111 mmol) followed by HOAc (4.51 mL) and the resulting mixture was stirred under Ar for 16 h and then poured into EtOAc (1.5 L) and 10% aq NaOH (200 mL), the mixture was shaken and the phases were separated. After an additional extraction with EtOAc , the combined organic phases were washed with satd aq NaCl, dried (K_2CO_3) concentrated and the residual oil was filtered through silica with CH_2Cl_2 to afford 20.13 g (72%) of a waxy solid.. MS ES (+) m/e = 352 (MH^+). ^1H NMR (CDCl_3): δ 4.02 (q, CH_2O

cis), 3.98 (q, CH₂O trans). Integration of the 2 quartets attributed to the ethoxycarbonyl CH₂s indicates a ca 45:55 ratio of the isomers.

c) Ethyl 4-dibenzylaminocyclohexanecarboxylate equilibration to favor the *trans* isomer)

5 The product of the preceding example (1.13 g, 3.05 mmol) was added to EtOH (Aldrich anhydrous) (8 mL) into which Na (75 mg) had been dissolved and the resulting solution was heated to EtOH reflux for 16 h, cooled, diluted with EtOAc, washed with H₂O, and then satd aq NaCl, dried (Na₂SO₄) and concentrated to afford 0.82g. MS ES (+) m/e = 352 (MH⁺). ¹H NMR (CDCl₃): d 4.02 (q, CH₂O cis), 3.98 (q, CH₂O trans).

10 Integration of the 2 quartets attributed to the ethoxycarbonyl CH₂s indicates a ca 1:4 ratio of *cis* to *trans* isomers.

d) 4-Dibenzylaminocyclohexylmethanol

The product of the preceding example (0.82 g, 2.21 mmol) was added to 1M LAH in Et₂O (3 mL, 3 mmol) and after a brief exotherm, the reaction was stirred at 23° for 16 h.

15 EtOAc (3 mL) was added dropwise and then H₂O (1 mL), 15% aq NaOH (1.5 mL), H₂O (3 mL) and more EtOAc (100 mL). The mixture was filtered, concentrated and flash chromatographed over silica (0-4% MeOH in CH₂Cl₂) to afford 0.60g (88%) of the title compound as a white solid. MS ES (+) m/e = 310 (MH⁺).

e) 4-Aminocyclohexylmethanol

20 The product of the preceding example (0.60 g, 1.94 mmol), Pd(OH)2 (0.3 g), and CH₃OH (20 mL) were combined and stirred under a balloon of H₂ for 1h, filtered and the filtrate was concentrated to afford 0.28 g (100%) of the title compound as a white solid. MS ES (+) m/e = 130 (MH⁺). ¹H NMR (CDCl₃): d 2.90 (m, CHNH₂ *cis*-NH₂), 2.65 (m, CHNH₂ *trans*-NH₂). Assignments based on peak widths for the 2 peaks and literature

25 (Schneider, W.; L:ehmann,K. *Tetrahedron Lett*, 1970, 4285-4288.). Integration of the 2 multiplets indicates a ca 1:4 ratio of *cis* to *trans*.

f) 2-Propylthiopyrimidine-4-carboxaldehyde [4-aminocyclohexylmethanol] imine

30 The product of the preceding example (0.24g, 1.86 mmol) and the product of example 1(b) (0.31g, 1.69 mmol) were combined and stirred under Ar 16 h. Concentration afforded a red oil. ¹H NMR was consistent with a 1:4 mixture of cyclohexane isomers. ¹H NMR (CDCl₃): d 8.23(s, 1, imine CH).

g) trans-1-(4-Hydroxymethylcyclohexyl)-4-(4-fluorophenyl)-5-[2-propylthio]pyrimidin-4-yl]imidazole

35 The product of the preceding example, the product of example 1(f) (0.54 g, 1.86 mmol), DMF (4 mL) and K₂CO₃ (259 mg, 1.86 mmol) were combined and stirred under Ar for 3 days. Et₂O (100 mL) was added and the precipitate was filtered off. The filtrate

was concentrated to a brown paste from which most of the DMF had been removed. Et₂O was added and a solid formed quickly from the initial solution and the resulting precipitate was washed with more Et₂O and dried, and flash chromatographed (10 g silica, 0-2% MeOH in CH₂Cl₂) to afford 207 mg (29% from the aldehyde used in the previous step) of a white solid. MS ES (+) m/e = 427 (MH⁺). ¹H NMR (CDCl₃) d 3.69 (d, 2, CHCH₂O, *cis*), 3.50 (d, 2, CHCH₂O, *trans*); integration indicated <6% *cis* isomer.

5 h) trans-1-(4-Hydroxymethylcyclohexyl)-4-(4-fluorophenyl)-5-[(2-propylsulfonyl)-pyrimidin-4-yl]imidazole

The product of the preceding example (200 mg, 0.47 mmol) was dissolved in THF (5 mL) and the solution was cooled to 4°. Oxone (0.694 g, 1.13 mmol) in H₂O was added dropwise. The resulting mixture was warmed to 23° and stirred for 18 h. EtOAc (100 mL) was added and the organic phase was washed with 10% aq NaOH, H₂O, and satd aq NaCl, dried (Na₂SO₄) and concentrated to afford 181 mg (84%). MS ES (+) m/e = 459 (MH⁺).

10 j) trans-1-(4-Hydroxymethylcyclohexyl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole 60% NaH in oil (40 mg, 1.0 mmol) was washed with THF, layered with more THF (3 mL) and phenol (188 mg, 2.0 mmol) was added. After 5 min the product of the preceding example (90 mg, 0.20 mmol) was added in THF (2 mL) and the mixture was stirred 30 min, diluted with EtOAc (50 mL) and washed with 10% aq NaOH (2X), H₂O, and satd aq NaCl, dried (Na₂SO₄), concentrated

15 20 and the residue was triturated with Et₂O to afford 35 mg (40%). MS ES (+) m/e = 445 (MH⁺). ¹H NMR (CDCl₃) d 3.62 (d, 2, CHCH₂O, *cis*), 3.42 (d, 2, CHCH₂O, *trans*); integration indicated <5% *cis* isomer.

Example 102

25 trans-1-(4-Hydroxymethylcyclohexyl)-4-(4-fluorophenyl)-5-[2-(4-fluorophenoxy)-pyrimidin-4-yl]imidazole

By the procedure of example 101 (j) except using 4-fluorophenol as the phenol. ES (+) m/e = 463 (MH⁺). ¹H NMR (CDCl₃) d 3.58 (d, 2, CHCH₂O, *cis*), 3.40 (d, 2, CHCH₂O, *trans*); integration indicated <5% *cis* isomer.

30

Using a resin based synthesis the following compounds have been prepared:

Example 103

Polymer-bound 2-thiopyrimidine-4-carboxaldehyde.

a) Polymer-bound 2-thiopyrimidine-4-carboxaldehyde dimethyl acetal.

35 Sodium 2-methylthiopyrimidine-4-carboxaldehyde dimethyl acetal (116 g, 560 mmol) was added to a mixture of Merrifield resin (1.4 mmol / g, 100 g, 140 mmol) in DMF

(500 mL). After stirring at ambient temperature for 18 h, the reaction mixture was filtered and the resin was washed successively with DMF, CH_2Cl_2 and MeOH and dried to afford a yellow-colored resin; yield 116 g (94%): MASNMR (CDCl_3) δ 8.5 (1H, pyrimidine H-6), 5.2 [1H, $(\text{MeO})_2\text{CH}-$], 3.3 [6H, $-(\text{OCH}_3)_2$].

5 b) Polymer-bound 2-thiopyrimidine-4-carboxaldehyde.

A mixture of Polymer-bound 2-thiopyrimidine-4-carboxaldehyde dimethyl acetal (135 g, 189 mmol maximum) in TFA (150 mL) was heated to reflux for 18 h. The reaction mixture was cooled to ambient temperature and filtered, washed successively with CH_2Cl_2 and 5% Et_3N in CH_2Cl_2 to afford the title material as an orange-yellow resin; yield 107 g (85%): MASNMR δ 9.9 (1H, CHO), 8.6 (1H, pyrimidine H-6).

Example 104

1-(Piperidin-4-yl)-4-(4-fluorophenoxy)-5-[2-(2,4-dimethylphenoxy)pyrimidin-4-yl]imidazole tris(trifluoroacetate)salt

15 a) Polymer-bound 2-thiopyrimidine-4-carboxaldehyde (N-t-butoxycarbonylpiperidine)imine.

A mixture of Polymer-bound 2-thiopyrimidine-4-carboxaldehyde (5.0 g, 7.0 mmol maximum) (the product of the preceding example) and 4-amino-N-t-butoxycarbonylpiperidine (1.6 g, 14 mmol) in CH_2Cl_2 (50 mL) was stirred for 18 h. The reaction mixture was filtered and the resin washed with CH_2Cl_2 to afford the title material.

b) Polymer-bound 1-(N-t-Butoxycarbonylpiperidinyl)-4-(4-fluorophenyl)-5-[(2-thio)pyrimidin-4-yl]imidazole.

A mixture of the entire sample of polymer-bound 2-thiopyrimidine-4-carboxaldehyde (N-t-butoxycarbonylpiperidine)imine from the preceding example (7.0 mmol maximum), 4-fluorophenyl-tolylsulfonomethylisocyanide (6.0 g, 21 mmol), and TBD (2.9 g, 21 mmol), in CH_2Cl_2 (50 mL) were stirred at 23° for 18 h. The reaction mixture was filtered and the resin was washed successively with CH_2Cl_2 , MeOH and CH_2Cl_2 to afford the title material.

c) Polymer-bound 1-(N-t-Butoxycarbonylpiperidinyl)-4-(4-fluorophenyl)-5-[(2-sulfonyl)pyrimidin-4-yl]imidazole.

A mixture of polymer-bound 1-N-t-butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[(2-thio)pyrimidin-4-yl]imidazole (1.5 g, 2.1 mmol maximum) and 3-peroxybenzoic acid (>95%, 0.54 g, 3.2 mmol) in CH_2Cl_2 (30 mL) was stirred at 23° for 18 h. The reaction mixture was filtered and washed with CH_2Cl_2 to afford the title material.

35 d) 1-N-t-Butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[2-(2,4-dimethylphenoxy)pyrimidin-4-yl]imidazole

2,4-Dimethylphenol (134 mg, 1.1 mmol) in dry THF (5 mL) was treated with sodium bis(trimethylsilyl)amide (1M in THF) (1 mL, 1 mmol) in an Ar filled shaker tube and the resulting solution was shaken 5 min. The product of the preceding example (0.4 g, 0.4 mmol maximum) was added to the tube and the mixture was shaken for 16 h. The 5 mixture was filtered and the resin was washed with CH₂Cl₂ (2 X 5 mL). The combined filtrates were concentrated and chromatographed on a 5 g plug of silica with 0 - 2% CH₂Cl₂ to afford 66 mg of the title compound as a white solid. ES+ MS *m/z* = 544 (MH⁺).
e) 1-(Piperidin-4-yl)-4-(4-fluorophenoxy)-5-[2-(2,4-dimethylphenoxy)pyrimidin-4-yl]imidazole tris(trifluoroacetate)salt. The product of the preceding example was combined 10 with TFA, stirred 30 min and the TFA was removed *in vacuo*. The residue was triturated with Et₂O, filtered and dried to afford 65 mg of the title compound as a white solid. ES+ MS *m/z* = 444 (MH⁺).
15

Example 105

15 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-isopropylphenoxy)pyrimidin-4-yl]imidazole.
a) 1-N-t-Butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[2-(4-isopropylphenoxy)pyrimidin-4-yl]imidazole By the procedure of example 104(d) except using 4-iso-propylphenol to afford 98 mg of the title compound as a white solid. ES+ MS 20 *m/z* = 558 (MH⁺).
b) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-isopropylphenoxy)pyrimidin-4-yl]imidazole. The product of the preceding example was combined with TFA, stirred 30 min and the TFA was removed *in vacuo*. The residue was dissolved in EtOAc (75 mL) and washed with 10% aq NaOH, H₂O, satd aq NaCl, dried (Na₂SO₄) and concentrated. The 25 resulting residue was crystallized from EtOAc/hexane to afford 44 mg of the title compound as a white solid. ES+ MS *m/z* = 458 (MH⁺).
25

Example 106

30 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyrimidin-4-yl]imidazole.
a) 1-N-t-Butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyrimidin-4-yl]imidazole By the procedure of example 104(d) except using 4- methylphenol to afford 139 mg of the title compound as a white solid. ES+ MS *m/z* = 530 (MH⁺).
35 b) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyrimidin-4-yl]imidazole. The product of the preceding example was reacted by the procedure of

example 105(b) to afford 60 mg of the title compound as a white solid. ES+ MS m/z = 430 (MH $^+$).

Example 107

5 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-t-butylphenoxy)pyrimidin-4-yl]imidazole.
 a) 1-N-t-Butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[2-(4-t-butylphenoxy)pyrimidin-4-yl]imidazole By the procedure of example 104(d) except using 4-t-butylphenol to afford 122 mg of the title compound as a white solid. ES+ MS m/z = 572 (MH $^+$).

10 b) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-t-butylphenoxy)pyrimidin-4-yl]imidazole. The product of the preceding example was reacted by the procedure of example 105(b) to afford 48 mg of the title compound as a white solid. ES+ MS m/z = 472 (MH $^+$).

15

Example 108

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-chlorophenoxy)pyrimidin-4-yl]imidazole
 a) 1-N-t-Butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[2-(4-chlorophenoxy)pyrimidin-4-yl]imidazole By the procedure of example 104(d) except using 4- chlorophenol to afford 114 mg of the title compound as a white solid. ES+ MS m/z = 550, 552 (MH $^+$).
 b) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-chlorophenoxy)pyrimidin-4-yl]imidazole The product of the preceding example was reacted by the procedure of example 105(b) to afford 51 mg of the title compound as a white solid. ES+ MS m/z = 450, 452 (MH $^+$).

25

Example 109

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-trifluoromethylphenoxy)pyrimidin-4-yl]imidazole
 a) 1-N-t-Butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[2-(4-trifluoromethylphenoxy)pyrimidin-4-yl]imidazole By the procedure of example 104(d) except using 4- trifluoromethylphenol to afford 100 mg of the title compound as a white solid. ES+ MS m/z = 584 (MH $^+$).
 b) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-trifluoromethylphenoxy)pyrimidin-4-yl]imidazole. The product of the preceding example was reacted by the procedure of example 105(b) to afford 42 mg of the title compound as a white solid. ES+ MS m/z = 484 (MH $^+$).

Example 110

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,4-dichlorophenoxy)pyrimidin-4-yl]imidazole.

a) 1-N-t-Butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[2-(3,4-dimethylphenoxy)pyrimidin-4-yl]imidazole By the procedure of example 104(d) except using 3,4-dichlorophenol to afford 129 mg of the title compound as a white solid. ES+ MS m/z = 584 (MH $^+$).

b) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,4-dichlorophenoxy)pyrimidin-4-yl]imidazole. The product of the preceding example was reacted by the procedure of example 105(b) to afford 56 mg of the title compound as a white solid. ES+ MS m/z = 484 (MH $^+$).

Example 111

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2,3-dimethylphenoxy)pyrimidin-4-yl]imidazole Tris(trifluoroacetate)salt.

a) 1-N-t-Butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[2-(2,3-dimethylphenoxy)pyrimidin-4-yl]imidazole By the procedure of example 104(d) except using 2,3-dimethylphenol to afford 54 mg of the title compound as a white solid. ES+ MS m/z = 544 (MH $^+$).

b) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2,3-dimethylphenoxy)pyrimidin-4-yl]imidazole Tris(trifluoroacetate)salt. The product of the preceding example was reacted by the procedure of example 104(e) to afford 89 mg of the title compound as a white solid. ES+ MS m/z = 444 (MH $^+$).

25

Example 112

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,4-dimethylphenoxy)pyrimidin-4-yl]imidazole tris(trifluoroacetate)salt

a) 1-N-t-Butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[2-(3,4-dimethylphenoxy)pyrimidin-4-yl]imidazole By the procedure of example 104(d) except using 3,4-dimethylphenol to afford 54 mg of the title compound as a white solid. ES+ MS m/z = 544 (MH $^+$).

b) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,4-dimethylphenoxy)pyrimidin-4-yl]imidazole Tris(trifluoroacetate)salt. The product of the preceding example was reacted by the procedure of example 104(e) to afford 89 mg of the title compound as a white solid. ES+ MS m/z = 444 (MH $^+$).

Example 113

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxypropylphenoxy)pyrimidin-4-yl]imidazole tris(trifluoroacetate)salt.

a) 1-N-t-Butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[2-(4-carboxypropylphenoxy)pyrimidin-4-yl]imidazole By the procedure of example 104(d) except using 4-carboxypropylphenol to afford 60 mg of the title compound as a white solid. ES+ MS m/z = 602 (MH $^+$).

5 b) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxypropylphenoxy)pyrimidin-4-yl]imidazole tris(trifluoroacetate)salt. The product of the preceding example was reacted by the procedure of example 104(e) to afford 78 mg of the title compound as a white solid. ES+ MS m/z = 502 (MH $^+$).

10

Example 114

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxyethylphenoxy)pyrimidin-4-yl]imidazole tris(trifluoroacetate)salt

a) 1-N-t-Butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[2-(4-carboxyethylphenoxy)pyrimidin-4-yl]imidazole By the procedure of example 104(d) except using 4-carboxyethylphenol to afford 55 mg of the title compound as a white solid. ES+ MS m/z = 588 (MH $^+$).

20 b) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxyethylphenoxy)pyrimidin-4-yl]imidazole tris(trifluoroacetate)salt
The product of the preceding example was reacted by the procedure of example 104(e) to afford 87 mg of the title compound as a white solid. ES+ MS m/z = 488 (MH $^+$).

25

Example 115

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,5-dimethylphenoxy)pyrimidin-4-yl]imidazole tris(trifluoroacetate)salt.

a) 1-N-t-Butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[2-(3,5-dimethylphenoxy)pyrimidin-4-yl]imidazole By the procedure of example 104(d) except using 3,5-dimethylphenol to afford 49 mg of the title compound as a white solid. ES+ MS m/z = 544 (MH $^+$).

30 b) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,5-dimethylphenoxy)pyrimidin-4-yl]imidazole tris(trifluoroacetate)salt. The product of the preceding example was reacted by the procedure of example 104(e) to afford 63 mg of the title compound as a white solid.

35 ES+ MS m/z = 444 (MH $^+$).

Example 116

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2,5-dimethylphenoxy)pyrimidin-4-yl]imidazole tris(trifluoroacetate)salt.

5 a) 1-N-t-Butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[2-(2,5-dimethylphenoxy)pyrimidin-4-yl]imidazole By the procedure of example 104(d) except using 2,5-dimethylphenol to afford 56 mg of the title compound as a white solid. ES+ MS m/z = 544 (MH^+).

10 b) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2,5-dimethylphenoxy)pyrimidin-4-yl]imidazole tris(trifluoroacetate)salt. The product of the preceding example was reacted by the procedure of example 104(e) to afford 77 mg of the title compound as a white solid. ES+ MS m/z = 444 (MH^+).

Example 117

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxymethylphenoxy)pyrimidin-4-yl]imidazole tris(trifluoroacetate)salt.

15 a) 1-N-t-Butoxycarbonylpiperidinyl-4-(4-fluorophenyl)-5-[2-(4-carboxymethylphenoxy)pyrimidin-4-yl]imidazole By the procedure of example 104(d) except using 4-carboxymethylphenol to afford 78 mg of the title compound as a white solid. ES+ MS m/z = 574 (MH^+).

20 b) 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxymethylphenoxy)pyrimidin-4-yl]imidazole tris(trifluoroacetate)salt. The product of the preceding example was reacted by the procedure of example 104(e) to afford 89 mg of the title compound as a white solid. ES+ MS m/z = 474 (MH^+).

25 Example 118

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxyphenoxy)pyrimidin-4-yl]imidazole Lithium salt

The product of the preceding example (57mg, 0.11 mmol) dissolved in 1:1 THF/CH₃OH (2 mL) was combined with LiOH (83 mg, 2 mmol) in H₂O (1 mL) and 30 stirred 2h. The organic solvents were removed *in vacuo* and the remaining aqueous solution was diluted with H₂O (5 mL) and added to a Vario 5 g RP-18 cartridge. Inorganic salts were removed by washing with H₂O and the product as the lithium salt was eluted in 50% CH₃OH in H₂O to afford 14 mg. ES+ MS m/z = 460 (MH^+).

35 Example 119

1-Isopropyl-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyrimidin-4-yl]imidazole

a) Polymer-bound 2-thiopyrimidine-4-carboxaldehyde(iso-propyl)imine Following the procedure of Example 104(a) except substituting iso-propylamine for 4-amino-N-t-butoxycarbonylpiperidine afforded the title material.

b) Polymer-bound 1-isopropyl-4-(4-fluorophenyl)-5-[(2-thio)pyrimidin-4-yl]imidazole

5 Following the procedure of Example 104(b) except using the product of the preceding example as the imine afforded the title material.

c) Polymer-bound 1-isopropyl-4-(4-fluorophenyl)-5-[(2-sulfonyl)pyrimidin-4-yl]imidazole Following the procedure of Example 104(c) except using the product of the preceding example, afforded the title material.

10 d) 1-Isopropyl-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)-pyrimidin-4-yl]imidazole The product of the preceding example, reacted by the procedure of example 104(d), using 4-methylphenol as the phenol afforded the title compound. ES+ MS *m/z* = 389 (MH⁺).

Example 120

15 Preparation of N-[2-[4-(4-fluorophenyl)-5-(2-Phenoxy)pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl] amides

Polymer-bound 2-thiopyrimidine-4-carboxaldehyde

a) Polymer-bound 2-thiopyrimidine-4-carboxaldehyde dimethyl acetal. Sodium 2-methylthiopyrimidine-4-carboxaldehyde dimethyl acetal (116 g, 560 mmol) was 20 added to a mixture of Merrifield resin (1.4 mmol / g, 100 g, 140 mmol) in DMF (500 mL). After stirring at ambient temperature for 18 h, the reaction mixture was filtered and the resin was washed successively with DMF, CH₂Cl₂ and MeOH and dried to afford a yellow-colored resin; yield 116 g (94%): MASNMR (CDCl₃) δ 8.5 (1H, pyrimidine H-6), 5.2 [1H, (MeO)₂CH-], 3.3 [6H, -(OCH₃)₂].

b) Polymer-bound 2-thiopyrimidine-4-carboxaldehyde. A mixture of Polymer-bound 2-thiopyrimidine-4-carboxaldehyde dimethyl acetal (135 g, 189 mmol maximum) in TFA (150 mL) was heated to reflux for 18 h. The reaction mixture was cooled to ambient temperature and filtered, washed successively with CH₂Cl₂ and 5% Et₃N in CH₂Cl₂ to afford the title material as a orange-yellow resin; yield 30 107 g (85%): MASNMR δ 9.9 (1H, CHO), 8.6 (1H, pyrimidine H-6).

Example 121

Polymer-bound N-[2-[4-Fluorophenyl]-5-(2-thiopyrimidin-4-yl)-1H-imidazol-1-yl]-2-ethyleneamine.

35 a) Polymer-bound 2-thiopyrimidine-4-carboxaldehyde (N-t-butoxycarbonylethylene)imine. A mixture of polymer-bound 2-thiopyrimidine-4-

carboxaldehyde (64.0 g, 80.0 mmol maximum) and 3-amino-N-t-butoxycarbonylethane (23.7 g, 150.0 mmol) in CH_2Cl_2 (500 mL) was stirred for 18h. The reaction mixture was filtered and the resin washed with CH_2Cl_2 to afford the title material. Yield = 75g.

5 b) Polymer-bound N-[2-[4-Fluorophenyl]-5-(2-thiopyrimidin-4-yl)-1H-imidazol-1-yl]-N-(t-butoxycarbonyl)ethylamine. A mixture of polymer-bound 2-thiopyrimidine-4-carboxaldehyde, N-[(t-butoxycarbonyl)ethylene]imine (75.0g, 75.3 mmol maximum), 4-fluorophenyl-tolylsulfonomethylisocyanide (54.5 g, 188.3 mmol), and TBD (26.2 g, 188.3 mmol), in CH_2Cl_2 (500 mL) was stirred at 23° for 10 h. The reaction mixture was filtered and the resin was washed successively with CH_2Cl_2 , MeOH and CH_2Cl_2 to afford the title material. yield 85 g.

c) Polymer-bound N-[2-[4-fluorophenyl]-5-(2-thiopyrimidin-4-yl)-1H-imidazol-1-yl]-ethyleneamine. A mixture of the entire sample of polymer-bound N-[2-[4-fluorophenyl]-5-(2-thiopyrimidin-4-yl)-1H-imidazol-1-yl]-N-(t-butoxycarbonyl)ethylamine (85g, 75.2 mmol) from example 2b in TFA (400 ml) was stirred at ambient temperature for 30 min. The reaction mixture was filtered, washed successively with CH_2Cl_2 and 5% Et_3N in CH_2Cl_2 to afford the title material as a orange-yellow resin; yield 78.3 g.

20

Example 122

N-[2-[4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]-1H-imidazol-1-yl]ethyl-3,4-dimethoxybenzamide

a) Polymer-bound N-[2-[4-fluorophenyl]-5-(2-thiopyrimidin-4-yl)-1H-imidazol-1-yl]-ethyl-3,4-dimethoxybenzamide. Triethylamine (1.8 mL, 1.3 g, 13 mmol) was added to a mixture of polymer-bound N-[2-[4-fluorophenyl]-5-(2-thiopyrimidin-4-yl)-1H-imidazol-1-yl]-ethyleneamine (1.9 g, 2.7 mmol) and 3,4-dimethoxybenzoyl chloride (2.7 g, 13 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was stirred for 18 h at ambient temperature and filtered. The resin was washed successively with CH_2Cl_2 , CH_2Cl_2 / MeOH (1:1) and MeOH to afford the title material.

b) Polymer-bound N-[2-[4-fluorophenyl]-5-[(2-sulfonyl)pyrimidin-4-yl]-1H-imidazol-1-yl]-ethyl-3,4-dimethoxybenzamide. 3-Choloroperoxybenzoic acid [(-80%), (1.5g, 6.8 mmol)] was added to polymer-bound N-[2-[4-fluorophenyl]-5-(2-thiopyrimidin-4-yl)-1H-imidazol-1-yl]-ethyl-3,4-dimethoxybenzamide (2.7 mmol) in CH_2Cl_2 (100 mL). After stirring for 2h at ambient temperature, the resin was filtered and washed with CH_2Cl_2 to afford the title material.

c) N-[2-[4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-3,4-dimethoxybenzamide. A solution of 2M sodium phenoxide in THF (2.25 mL, 4.5 mL) was added to polymer-bound N-[2-[4-fluorophenyl)-5-[(2-sulfonyl)pyrimidin-4-yl]-1H-imidazol-1-yl]-ethyl-3,4-dimethoxybenzamide (0.90 mmol) in THF (20 mL). After stirring for 18h at room temperature, the reaction mixture was poured into 2.5 N NaOH, extracted with ethyl acetate and the layers were separated. The organic phase was filtered to remove resin and washed twice with 2.5 N NaOH, brine and dried ($MgSO_4$) and the solvents evaporated. The residue was vacuum filtered through a pad of silica gel eluting successively with 100:1 and 50:1 CH_2Cl_2 / MeOH. Fractions containing the desired product were concentrated and the residue was triturated with ether to afford the title compound as an off-white solid; yield 0.078 g (16% overall): ESMS m/z = 540 ($M + H^+$).

15 The following compounds were prepared using the same procedure as described in Example 122 except substituting the appropriate acid chloride and phenol (or alcohol) for 3,4-dimethoxybenzoyl chloride and phenol, respectively.

Example 123: N-[2-[4-(4-fluorophenyl)-5-[2-(4-fluoro)phenoxy]pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-3,4-dimethoxybenzamide.

20 Example 124: N-[2-[4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide.

Example 125: N-[2-[4-(4-fluorophenyl)-5-[(2-trifluoroethoxy)pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide.

25 Example 126: N-[2-[4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide.

Example 127: N-[2-[4-(4-fluorophenyl)-5-[2-(4-benzyloxyphenoxy)pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide.

Example 128: N-[2-[4-(4-fluorophenyl)-5-[(2-cyclohexyl)ethoxy]pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide.

30 Example 129: N-[2-[4-(4-fluorophenyl)-5-[2-(4-isopropyl)phenoxy]pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide.

Adaptation of the above methodology to the array afforded the compounds listed herein with their respective mass spec data in the accompanying Table 1 shown below. The X in the table designates a compound for which data was not obtained.

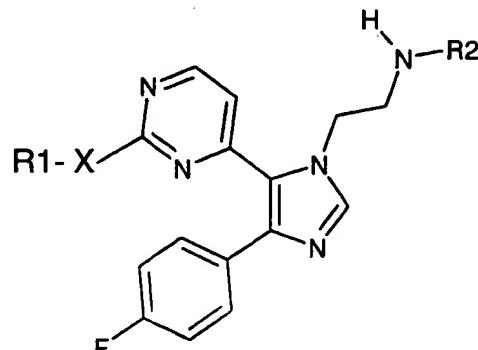
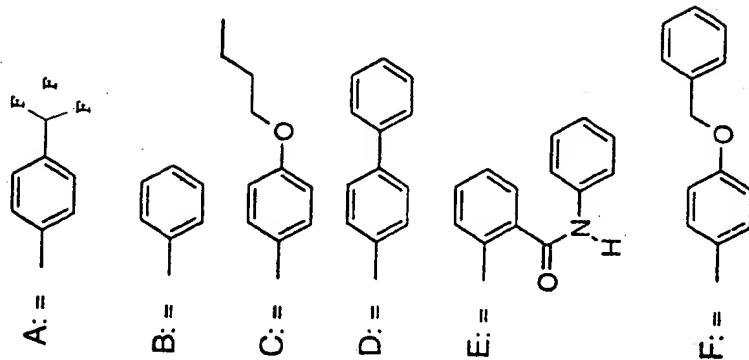
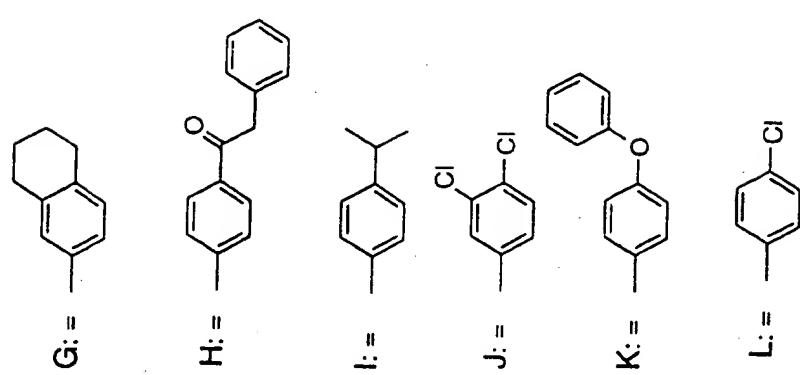
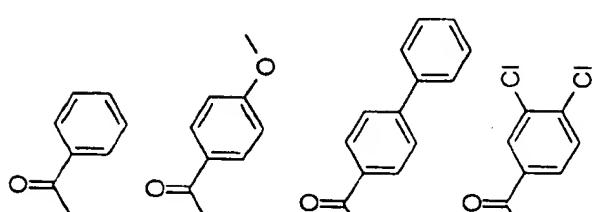
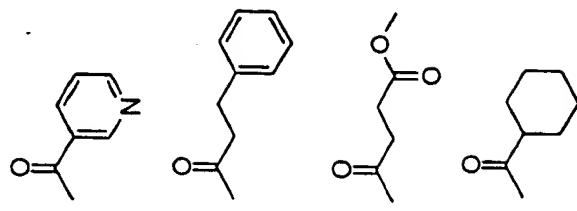


Table 1
(Characterization Data for Array - wherein X is Oxygen)
[m/z (M + H⁺)]

R1	A	B	C	D	E	F	G	H	I	J	K	L
R2												
I	549	549	480	556	599	586	534	598	522	549	572	X
II	578	510	582	586	629	616	564	628	552	579	602	544
III	624	556	628	632	675	662	610	674	598	625	648	591
IV	617	549	621	625	X	655	603	667	591	618	641	583
V	549	481	553	557	X	587	535	599	523	550	573	515
VI	576	508	580	584	X	614	562	626	550	577	X	543
VII	X	X	X	X	X	X	X	X				
VIII	554	486	558	562	X	592	510	604	528	555	578	X



All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

5.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the 10 preceding description, utilize the present invention to its fullest extent. Therefore, the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed is:

1. A compound, or pharmaceutically acceptable salt which is:
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[(2-acetamidophenoxy)pyrimidin-4-yl]imidazole
5
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[(3-propionamidophenoxy)pyrimidin-4-yl]imidazole
1-Cyclohexyl-4-(4-fluorophenyl)-5-[(2-phenoxy)pyrimidin-4-yl]imidazole
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(2,6-dimethylphenoxy)pyrimidin-4-yl]imidazole
10
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(2-methylphenoxy)pyrimidin-4-yl]imidazole
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(2,6-dimethyl-4-chlorophenoxy)pyrimidin-4-yl]imidazole
15
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(indol-4-yloxy)pyrimidin-4-yl]imidazole
1-Cyclopropyl-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole
1-Isopropyl-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole
1-Cyclopentyl-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole
(+/-)-1-(1-Hydroxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl)imidazole
20
3-[4-(4-Fluorophenyl)-5-[(2-phenoxy)pyrimidin-4-yl]imidazol-1-yl] propionitrile
(R)-(1-Hydroxy-3-phenylprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole
(S)-(1-Hydroxy-3-phenylprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole
25
(+/-)-1-(1-Phenoxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(3-piperazin-1-ylacetamido)phenoxy]pyrimidin-4-yl]imidazole; or
30
1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(3-piperazin-1-ylamidophenoxy)pyrimidin-4-yl]imidazole;
or a pharmaceutically acceptable salt thereof.

2. A compound, or pharmaceutically acceptable salt thereof, which is:

1-Isopropyl-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)-pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxyphenoxy)pyrimidin-4-yl]imidazole

5 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxymethylphenoxy) pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2,5-dimethylphenoxy)pyrimidin-4-yl]imidazole

10 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,5-dimethylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxyethylphenoxy)pyrimidin-4-yl]imidazole

15 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxypropylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,4-dimethylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2,3-dimethylphenoxy)pyrimidin-4-yl]imidazole

20 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,4-dichlorophenoxy)pyrimidin-4-yl]imidazole.

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-trifluoromethylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-chlorophenoxy)pyrimidin-4-yl]imidazole

25 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-t-butylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyrimidin-4-yl]imidazole.

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-isopropylphenoxy)pyrimidin-4-yl]imidazole.

30 1-(Piperidin-4-yl)-4-(4-fluorophenoxy)-5-[2-(2,4-dimethylphenoxy)pyrimidin-4-yl]imidazole

1-(4-Hydroxymethylcyclohexyl)-4-(4-fluorophenyl)-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]imidazole

1-(4-Hydroxymethylcyclohexyl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-methylcarboxamido-phenoxy)pyrimidin-4-yl]imidazole

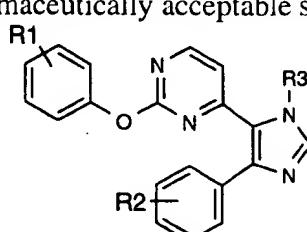
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-carboxamidophenoxy)pyrimidin-4-yl]imidazole

5 1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-dimethylcarboxamido-phenoxy)pyrimidin-4-yl]imidazole

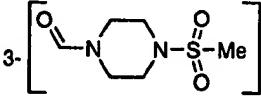
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-piperidinylcarboxamido-phenoxy)pyrimidin-4-yl]imidazole; or

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-isopropylcarboxamido-phenoxy)pyrimidin-4-yl]imidazole.

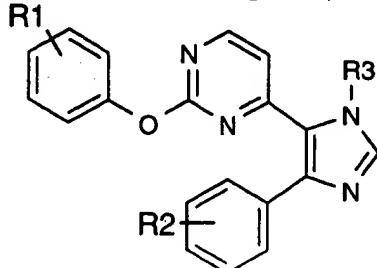
10 3. A compound, or pharmaceutically acceptable salt thereof, which is:

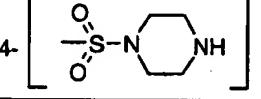
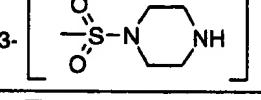
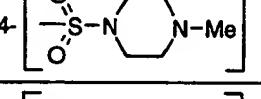
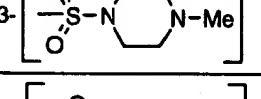
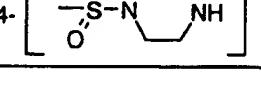


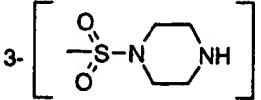
R1	R2	R3
4-CONHMe	4-F	piperidin-4-yl
4-CON(Me) ₂	4-F	piperidin-4-yl
4-CON(CH ₂) ₄	4-F	piperidin-4-yl
3-CON(CH ₂) ₄	4-F	piperidin-4-yl
4-CON(CH ₂) ₅	4-F	piperidin-4-yl
4-[]	4-F	piperidin-4-yl
3-[]	4-Cl	piperidin-4-yl
4-[4-F	piperidin-4-yl
3-[4-F	piperidin-4-yl
4-[4-F	piperidin-4-yl

3- 	4-F	piperidin-4-yl
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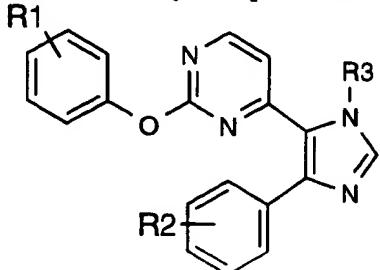
4. A compound, or pharmaceutically acceptable salt thereof, which is:



R1	R2	R3
4-SO ₂ NHMe	4-F	piperidin-4-yl
3- SO ₂ NH ₂	4-F	piperidin-4-yl
3- SO ₂ NHMe	4-F	piperidin-4-yl
4- SO ₂ N(Me) ₂	4-F	piperidin-4-yl
3- SO ₂ N(Me) ₂	4-F	piperidin-4-yl
4- SO ₂ N(CH ₂) ₄	4-F	piperidin-4-yl
3- SO ₂ N(CH ₂) ₄	4-F	piperidin-4-yl
4- SO ₂ N(CH ₂) ₅	4-F	piperidin-4-yl
3- SO ₂ N(CH ₂) ₅	4-F	piperidin-4-yl
4- 	4-F	piperidin-4-yl
3- 	4-F	piperidin-4-yl
4- 	4-F	piperidin-4-yl
3- 	4-F	piperidin-4-yl
4- 	4-H	piperidin-4-yl

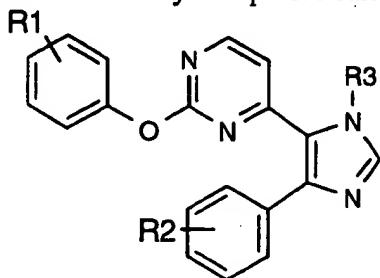
3- 	3-Cl	piperidin-4-yl
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5. A compound, or pharmaceutically acceptable salt thereof, which is:



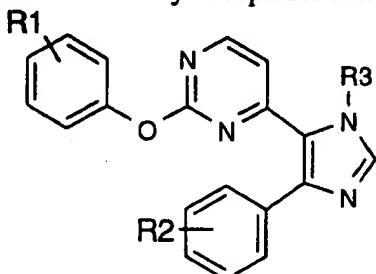
R1	R2	R3
4-NHSO ₂ Me	4-F	piperidin-4-yl
3-NHSO ₂ Me	4-F	piperidin-4-yl
3-NHSO ₂ Ph	4-F	piperidin-4-yl
4-NMeSO ₂ Me	4-F	piperidin-4-yl
3-NMeSO ₂ Me	4-F	piperidin-4-yl
3-NMeSO ₂ Ph	4-F	piperidin-4-yl
3-SO ₂ Me	4-F	piperidin-4-yl
3-SO ₂ Et	4-F	piperidin-4-yl
4-SO ₂ Et	4-F	piperidin-4-yl
3-SO ₂ NHCH ₂ CH ₂ N(Me) ₂	4-F	piperidin-4-yl
4-SO ₂ NHCH ₂ CH ₂ N(Me) ₂	4-F	piperidin-4-yl
4-NHSO ₂ Ph	4-F	piperidin-4-yl
4-NHSO ₂ Me	3-Cl	piperidin-4-yl
4-NHSO ₂ Me	4-H	piperidin-4-yl
3-SO ₂ Me	3-Cl	piperidin-4-yl

6. A compound, or pharmaceutically acceptable salt thereof, which is:



R1	R2	R3
4-CH ₂ CONHMe	4-F	piperidin-4-yl
3-CH ₂ CONH ₂	4-F	piperidin-4-yl
3-CH ₂ CONHMe	4-F	piperidin-4-yl
4-CH ₂ CON(Me) ₂	4-F	piperidin-4-yl
3-CH ₂ CON(Me) ₂	4-F	piperidin-4-yl
4-CH ₂ CON(CH ₂) ₄	4-F	piperidin-4-yl
3-CH ₂ CON(CH ₂) ₄	4-F	piperidin-4-yl
4-CH ₂ CON(CH ₂) ₅	4-F	piperidin-4-yl
3-CH ₂ CON(CH ₂) ₅	4-F	piperidin-4-yl
4-[]	4-F	piperidin-4-yl
3-[]	3-Cl	piperidin-4-yl
4-[]	4-F	piperidin-4-yl
3-[]	4-F	piperidin-4-yl
4-[]	4-F	piperidin-4-yl
3-[]	4-F	piperidin-4-yl

7. A compound, or pharmaceutically acceptable salt thereof, which is:



R1	R2	R3
4-CONHMe	4-Me	piperidin-4-yl
3-CONH ₂	4-Me	piperidin-4-yl
3-CONHMe	4-Me	piperidin-4-yl
4-CON(Me) ₂	4-Me	piperidin-4-yl
3-CON(Me) ₂	4-Me	piperidin-4-yl
4-NHSO ₂ Me	4-Me	piperidin-4-yl
3-NHSO ₂ Me	4-Me	piperidin-4-yl
3-NHSO ₂ Ph	4-Me	piperidin-4-yl
3-SO ₂ Me	4-Me	piperidin-4-yl
3-SO ₂ Et	4-Me	piperidin-4-yl
4-SO ₂ Et	4-Me	piperidin-4-yl
3-SO ₂ NHCH ₂ CH ₂ N(Me) ₂	4-Me	piperidin-4-yl
4-CH ₂ CONH ₂	4-Me	piperidin-4-yl
3-CH ₂ CONH ₂	4-Me	piperidin-4-yl
3-CH ₂ CONMe ₂	4-F	piperidin-4-yl

5 8. A pharmaceutical composition comprising an effective amount of a compound according to any of Claims 1 to 7 and a pharmaceutically acceptable carrier or diluent.

9. A method of treating a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, which method comprises administering to said mammal an effective amount of a compound according to any of Claims 3 to 7.

10. The method according to Claim 9 wherein the CSBP/RK/p38 kinase mediated disease is psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic condition, 5 sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, congestive heart failure, chronic renal failure, angiogenesis 10 & related processes, thrombosis, glomerularnephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, eczema, contact dermititis, psoriasis, sunburn, or conjunctivitis.

15 11. A method of treating a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, which method comprises administering to said mammal an effective amount of a compound which is:

1-**(4-Piperidinyl)-4-(4-fluorophenyl)-5-[(2-acetamidophenoxy)pyrimidin-4-yl]imidazole**

20 1-**(4-Piperidinyl)-4-(4-fluorophenyl)-5-[(3-propionamidophenoxy)pyrimidin-4-yl]imidazole**

1-Cyclohexyl-4-(4-fluorophenyl)-5-[(2-phenoxy)pyrimidin-4-yl]imidazole

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(2,6-dimethylphenoxy)pyrimidin-4-yl]imidazole

25 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(2-methylphenoxy)pyrimidin-4-yl]imidazole

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(2,6-dimethyl-4-chlorophenoxy)pyrimidin-4-yl]imidazole

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(indol-4-yloxy)pyrimidin-4-yl]imidazole

30 1-Cyclopropyl-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

1-Isopropyl-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

1-Cyclopentyl-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

(+/-)-1-(1-Hydroxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

35 3-[4-(4-Fluorophenyl)-5-[(2-phenoxy)pyrimidin-4-yl]imidazol-1-yl] propionitrile

(R)-(1-Hydroxy-3-phenylprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl)imidazole

(S)-(1-Hydroxy-3-phenylprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl)imidazole

5 (+/-)-1-(1-Phenoxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-(phenoxy)pyrimidin-4-yl)imidazole

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(3-piperazin-1-ylacetamido)phenoxy-pyrimidin-4-yl]imidazole; or

1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[2-(3-piperazin-1-ylamidophenoxy)-pyrimidin-4-yl]imidazole;

10 or a pharmaceutically acceptable salt thereof.

12. The method according to Claim 11 wherein the CSBP/RK/p38 kinase mediated disease is psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic condition, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, congestive heart failure, chronic renal failure, angiogenesis & related processes, thrombosis, glomerularnephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, eczema, contact dermititis, psoriasis, 20 sunburn, or conjunctivitis.

13. A method of treating a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, which method comprises administering to said mammal an effective amount of a compound which is:

30 1-Isopropyl-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)-pyrimidin-4-yl]imidazole)
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxyphenoxy)pyrimidin-4-yl]imidazole
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxymethylphenoxy) pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2,5-dimethylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,5-dimethylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxyethylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-carboxypropylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,4-dimethylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(2,3-dimethylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3,4-dichlorophenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-trifluoromethylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-chlorophenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-t-butylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(4-isopropylphenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenoxy)-5-[2-(2,4-dimethylphenoxy)pyrimidin-4-yl]imidazole

1-(4-Hydroxymethylcyclohexyl)-4-(4-fluorophenyl)-5-[2-(4-fluorophenoxy)pyrimidin-4-yl]imidazole

1-(4-Hydroxymethylcyclohexyl)-4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-methylcarboxamido-phenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-carboxamidophenoxy)pyrimidin-4-yl]imidazole

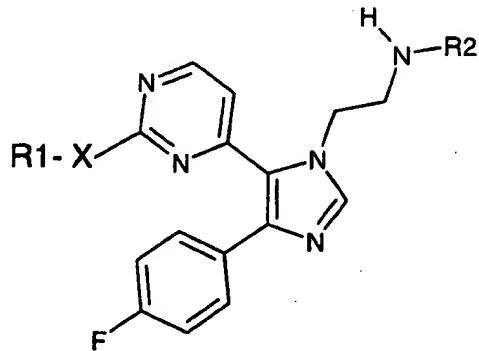
1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-dimethylcarboxamido-phenoxy)pyrimidin-4-yl]imidazole

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-piperidinylcarboxamido-phenoxy)pyrimidin-4-yl]imidazole; or

1-(Piperidin-4-yl)-4-(4-fluorophenyl)-5-[2-(3-N-isopropyl-carboxamido-phenoxy)pyrimidin-4-yl]imidazole.

14. The method according to Claim 13 wherein the CSBP/RK/p38 kinase mediated disease is psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic condition, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, congestive heart failure, chronic renal failure, angiogenesis & related processes, thrombosis, glomerularnephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, eczema, contact dermititis, psoriasis, sunburn, or conjunctivitis.

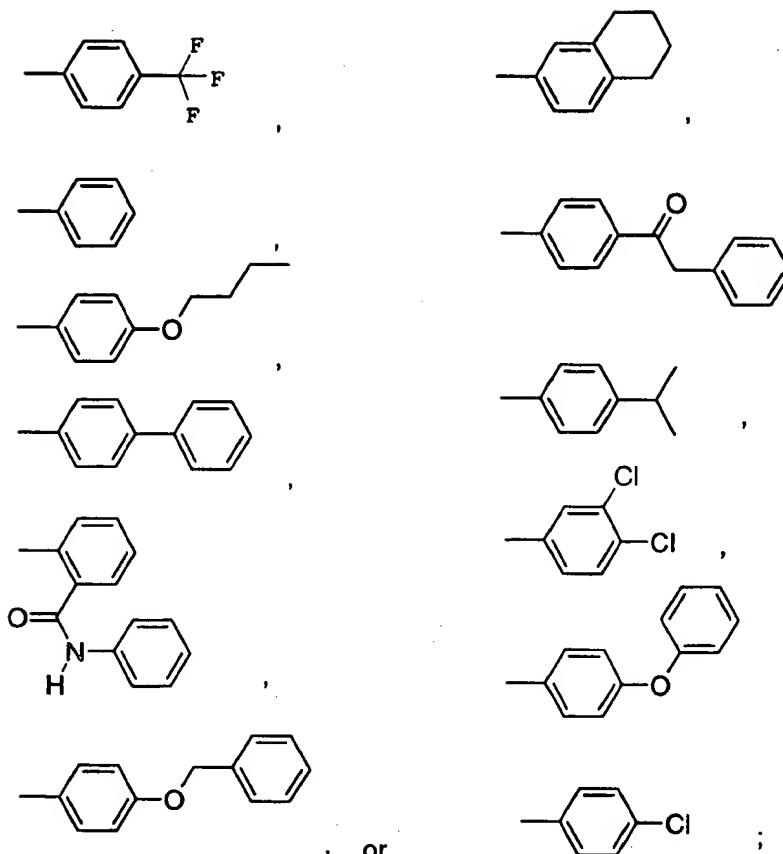
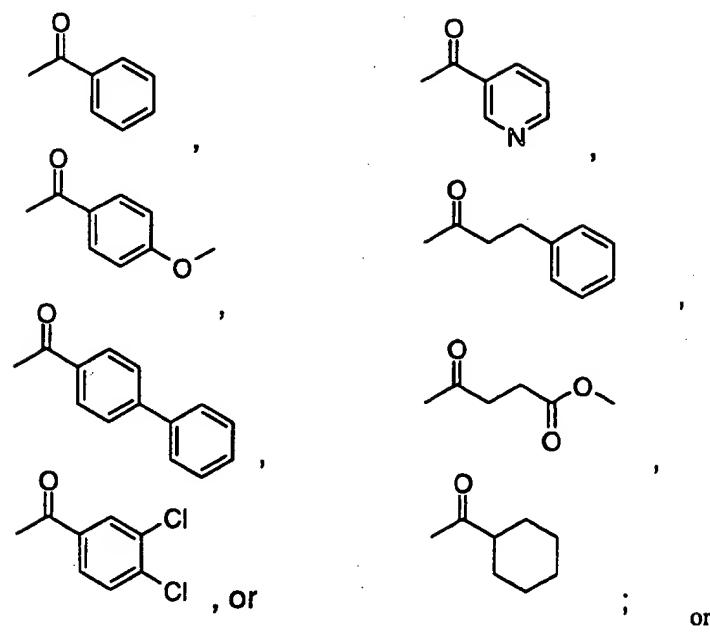
15. A compound of the formula:



20 wherein

X is oxygen or sulfur;

R1 is

 R_2 is

a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising an effective amount of a compound according to Claim 15 and a pharmaceutically acceptable carrier or diluent.

17. A method of treating a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, which method comprises administering to said mammal an effective amount of a compound according to Claim 15.

18. The method according to Claim 17 wherein the CSBP/RK/p38 kinase mediated disease is psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic condition, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, congestive heart failure, chronic renal failure, angiogenesis & related processes, thrombosis, glomerularnephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, eczema, contact dermititis, psoriasis, sunburn, or conjunctivitis.

19. A compound which is:

N-[2-[4-(4-fluorophenyl)-5-[2-(4-fluoro)phenoxy]pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-3,4-dimethoxybenzamide

25 N-[2-[4-(4-fluorophenyl)-5-(2-phenoxy)pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide

N-[2-[4-(4-fluorophenyl)-5-[(2-trifluoroethoxy)pyrimidin-4-yl]]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide

30 N-[2-[4-(4-fluorophenyl)-5-[2-(4-methylphenoxy)pyrimidin-4-yl]]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide

N-[2-[4-(4-fluorophenyl)-5-[2-(4-benzyloxyphenoxy)pyrimidin-4-yl]]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide

N-[2-[4-(4-fluorophenyl)-5-[(2-cyclohexyl)ethoxy]pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide; or

N-[2-[4-(4-fluorophenyl)-5-[2-(4-isopropyl)phenoxy]pyrimidin-4-yl]-1H-imidazo-1-yl]ethyl-2-methoxyacetamide; or
a pharmaceutically acceptable salt thereof.

- 5 20. A pharmaceutical composition comprising a compound according to Claim 18, and a pharmaceutically acceptable carrier or diluent.
- 10 21. A method of treating a CSBP/RK/p38 kinase mediated disease in a mammal in need thereof, which method comprises administering to said mammal an effective amount of a compound according to Claim 19.
- 15 22. The method according to Claim 21 wherein the CSBP/RK/p38 kinase mediated disease is psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic condition, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, congestive heart failure, chronic renal failure, angiogenesis & related processes, thrombosis, glomerularnephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, eczema, contact dermititis, psoriasis, sunburn, or conjunctivitis.
- 20 23. A compound of Formula (A) as shown and described herein.
- 25 24. A compound of Formula (B) as shown and described herein.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/13805

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/445; 31/535 C07D 401/14; 413/14
 US CL : 514/235.8, 318; 544/124; 546/194

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/235.8, 318; 544/124; 546/194

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	US 5,756,499 A (ADAMS et al) 26 May 1998, claims 1-39.	1-24
A	US 5,593,991 A (ADAMS et al) 14 January 1997, claims 1-28.	1-24
A	US 5,593,992 A (ADAMS et al) 14 January 1997, claims 1-41.	1-24
A	US 4,503,065 A (WILKERSON) 05 March 1985, claims 1-7.	1-24
A	US 4,447,431 A (SALLMANN) 08 May 1984, claims 1-17.	1-24
A	US 4,822,805 A (TAKASUGI et al) 18 April 1989, claims 1-9.	1-24

Further documents are listed in the continuation of Box C. See patent family annex.

• Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"a"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

17 NOVEMBER 1998

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